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IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF UTAH, CENTRAL DIVISION

UNIVERSITY OF UTAH RESEARCH FOUNDATION, et. al., Plaintiffs, vs. AMBRY GENETICS CORPORATION, Defendant. ——————————————— UNIVERSITY OF UTAH RESEARCH FOUNDATION, et. al., Plaintiffs, vs. GENE BY GENE, LTD., Defendant.	**PLAINTIFFS' REPLY MEMORANDUM IN SUPPORT OF MOTION FOR PRELIMINARY INJUNCTIVE RELIEF** Case No. 2:13-cv-00640-RJS Judge Robert J. Shelby

Plaintiffs University of Utah Research Foundation, the Trustees of the University of Pennsylvania, HSC Research and Development Limited Partnership, Endorecherche, Inc., and Myriad Genetics, Inc. (collectively, "Myriad") hereby submit their Reply in Support of their Motion for Preliminary Injunctive Relief.

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INTRODUCTION

The NBC Nightly News broadcast on September 13, 1994, began with what it described as "one of the most important breakthroughs in breast cancer research in years."[1] The announcement came from an unlikely source, a group of researchers in Utah who, in conjunction with colleagues across the United States and Canada, claimed to have discovered the long sought after breast cancer predisposition gene, *BRCA1*. In the ensuing days, *The Wall Street Journal* would herald the event as "a landmark discovery,"[2] and *The New York Times* would analogize the event to "[c]apturing a genetic trophy so ferociously coveted and loudly heralded that it had taken on a near-mythic aura."[3] Two days later, *BioWorld Today* described the discovery as "a clear scientific triumph," and quoted National Institutes of Health officials as "saying it represented the 'best in American science.'"[4]

But the discovery was only the first step. Years of additional work and hundreds of millions of dollars of additional investment would be required to make practical use of the new information and to develop tests and procedures to benefit those afflicted or potentially afflicted by hereditary breast cancer. The same news sources reported that *BRCA1* "is an especially large gene,"[5] and that "the researchers caution that they are still far from developing a diagnostic test" because "the gene turns out to be exceptionally long—much longer than they had expected—and to be susceptible to many different types of mutations up and down its span. That makes the task

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[1] NBC-TV, NBC Nightly News, Sept. 13, 1994 (transcript attached as Ex. A to Declaration of David G. Mangum ("Mangum Decl.")).

[2] The Wall Street Journal (Sept. 14, 1994) (Mangum Decl. Ex. B).

[3] The New York Times (Sept. 15, 1994) (Mangum Decl. Ex. C).

[4] BioWorld Today, Vol. 5, No. 179 (Sept. 15, 1994) (Mangum Decl. Ex. D).

[5] Wall Street Journal (Mangum Decl. Ex. B).

of devising a screening test to detect the mutations a considerable challenge."[6] Myriad's scientists did not shy away from that challenge. They persisted with the arduous, long, and expensive process of applying their new-found knowledge, and developing and bringing to market tests that have saved countless lives.

Now that the work is complete, what do Defendants (and their amici) believe that Myriad deserves from a patent perspective for this "landmark" and "wondrous" work? Nothing. In their view, Myriad's work to develop its eagerly anticipated test reduces itself to a "law of nature," and application of known and obvious techniques to that law. Fortunately, the law is not so jaundiced.

Defendants advance a scattershot of issues they claim should deprive Myriad of the benefit of its work, and the exclusivity and injunctive relief the patent laws provide. The quantity of the issues raised, however, does not detract from the quality of Myriad's work and ingenuity. The patent law provides patentees 20-years of exclusivity on their inventions. Given the short remaining terms of many of Myriad's patents, the only way that exclusivity can be preserved and Myriad rewarded with the benefit of its bargain under the patent laws, is by entry of a preliminary injunction.

A preliminary injunction is warranted here because (1) Myriad is likely to prevail on the merits of its infringement claims against Defendants, (2) Myriad will suffer irreparable injury in the absence of injunctive relief, (3) the balance of the harms is in Myriad's favor, and (4) the public interest is furthered by enforcement of Myriad's patent rights.

The likelihood of success on the merits element in this case consists of three sub-elements: (1) the confirmed patent eligibility of the claims asserted by Myriad as expounded by

[6] New York Times (Mangum Decl. Ex. C).

recent Supreme Court and Federal Circuit authority, (2) Defendants' clear infringement of those claims, and (3) the absence of any serious question regarding the validity of Myriad's asserted patent claims. Importantly, each of these items—patent infringement, eligibility, and validity—must be examined on a claim by claim basis. Accordingly, to find a likelihood of success on the merits, this Court need only conclude that any one of Myriad's asserted patent claims is patentable, valid, and infringed. Stated alternatively, Defendants must persuade this Court that no single patent claim is patent-eligible, infringed, and valid. This task is made even more difficult because of the narrowness and precision of the claims Myriad asserts: composition of matter claims directed at "a pair of primers," specifically designed for use with the BRCA1 and BRCA2 gene sequence discovered by Myriad, that clearly do not exist in nature and serve entirely different functions than naturally occurring DNA; and method claims similarly limited to application of Myriad's newly discovered, BRCA1 and BRCA2 specific knowledge.

The remaining elements of irreparable harm, balance of the hardships, and public interest considerations likewise favor entry of an injunction. As patentee, Myriad is entitled to the benefit of its remaining limited patent term, and Defendants have not overcome Myriad's showing that the price erosion and loss of market share Myriad would suffer absent an injunction would be irreparable under existing authority, or that the public interest in accessible, affordable BRCA testing is amply met by Myriad.

RESPONSE TO STATEMENT OF FACTS

Myriad responds to Defendants' Statement of Facts as follows.

1. The information contained in a segment of DNA is contained in the sequence of nucleotides of that segment. E.g., Pribnow Decl., ¶¶ 22-27; Tait Decl., ¶ 32.

RESPONSE: Myriad disputes paragraph number 1. DNA and any segment of DNA are a collection of molecules, including individual nucleotides, that create a chemical compound. DNA and any segment of DNA do not contain "information" (like computer or computer storage device or any analogous device). *See* Roa Decl. at ¶¶ 4, 6-12, 16-17.

2. Segments of "natural" DNA in the human body are indistinguishable from identical DNA segments chemically synthesized, both structurally and in the information the two types of segments contain. E.g., Pribnow Decl., ¶¶ 19, 52-54.

RESPONSE: Myriad disputes paragraph number 2. See response to paragraph 1 above. Also, a segment of synthetically made DNA creates a different chemical compound than exists in the "natural" DNA in the human chromosomes because they both consist of a different overall collection of molecules. Different collections of molecules create different chemical compounds with different properties. *See* Roa Decl. at ¶¶ 4, 6-12, 16-17.

3. Single-stranded DNA exists in nature during the steps of DNA replication and DNA transcription, processes that occur literally trillions of times in the human body. E.g., Pribnow Decl., ¶¶ 35-38, 43, 81.

RESPONSE: Myriad disputes paragraph number 3. The DNA in replication and transcription is not single-stranded because, at best, only a small part of the DNA molecule is in that form at any given time. Each end of that small part of DNA remains connected and chemically bonded to an extensive double-strand of DNA stretching to each respective end of the

human genome, and thus that DNA molecule is not single-stranded. *See* Roa Decl. at ¶¶ 6-7, 16-17; Prinbow Decl. at ¶ 36.

4. Where a chemically synthesized DNA segment and the natural DNA segment have the same nucleotide sequence, the types of DNA segments are indistinguishable. E.g., Pribnow Decl., ¶¶ 52-54.

RESPONSE: Myriad disputes paragraph number 4. See response to paragraph 2 above. *See* Roa Decl. at ¶¶ 4, 6-12, 16-17.

5. The natural law of Watson-Crick base pairing requires that the following nucleotides in opposite DNA segments pair as follows: adenine (A) and thymine (T); guanine (G) and cytosine (C). E.g., Pribnow Decl., ¶¶ 28-32; Tait Decl., ¶ 22.

RESPONSE: Undisputed.

6. DNA segments that are complementary will associate (hybridize) through Watson-Crick base pairing regardless of whether both DNA segments are "natural" DNA found in the body, DNA segments chemically synthesized in the laboratory, or a combination of the two. E.g., Pribnow Decl., ¶¶ 28-38, 66-68, 91.

RESPONSE: Undisputed.

7. A PCR synthesized copy ("amplicon") of genomic DNA is indistinguishable from the genomic DNA segment that is used as a template. E.g., Pribnow Decl., ¶¶ 16, 58, 64, 68, 70; Tait Decl. ¶¶ 29-32.

RESPONSE: Myriad disputes paragraph number 7. An amplicon is a very different molecule from the genomic DNA segment used as a template because the amplicon is a shorter segment of DNA, has different nucleotides on each end, and thus is an entirely different molecule and an entirely different chemical compound. *See* Roa Decl. at ¶¶ 6-12.

8. "Complementary DNA," or "cDNA," is a term of art that means a DNA molecule chemically synthesized from a messenger RNA ("mRNA") transcript from which the introns have been removed. E.g., Pribnow Decl., ¶¶ 78, 82.

RESPONSE: Undisputed.

9. "Complementary DNA" and "primers" do not refer to the same type of molecule, because primers are not synthesized from a mRNA from which the introns have been removed. E.g., Pribnow Decl., ¶ 78.

RESPONSE: Undisputed.

10. PCR was well known in the art by August 12, 1994. E.g., '999 patent at col. 17 ll. 14-34, col. 25 ll. 52-57; Pribnow Decl., ¶¶ 74, 75; Tait Decl., ¶ 29.

11. DNA sequencing was well known in the art by August 12, 1994. E.g., '999 patent at col. 14 ll. 1-7, col. 17 ll. 14-34; Tait Decl., ¶ 35.

12. Using probes to hybridize to DNA sequences was well known in the art by August 12, 1994. E.g., '999 patent at col. 15 ll. 9-20, col. 17 ll. 14-34, col. 21 l. 37 - col. 22 l. 27.

RESPONSE TO PARAGRAPHS 10-12: Myriad admits paragraph numbers 10-12 but only to the extent that PCR, DNA sequencing, and/or using probes to hybridize DNA sequences had been applied to certain genes before August 12, 1994, but denies that it was well known or even possible to apply those techniques to the BRCA1 or BRCA2 genes. The sequence of those genes had to be known first before any of those techniques could be applied to them. The nucleotide sequences of those genes were not known until Plaintiffs discovered them and disclosed them in their patent applications. The earliest patent application disclosing the BRCA1 sequences was filed on August 12, 1994, and the earliest patent application disclosing the BRCA2 sequence was filed on December 18, 1995. *See* '282 patent at cover page (filing date),

Figs. 10A-10H & cols. 67-90 (disclosing the full BRCA1 sequence); '492 patent cover page (filing date), Figs. 3A-3D & cols. 59-100 (disclosing the full BRCA2 sequence).

13. Abel (1993) and Anderson (1993) each discloses a pair of PCR primers that are derived from human chromosome 17q. The primer pairs were used to amplify intragenic marker D17S855. Gregory Decl., ¶¶ 60-62, 68-70, Exs. A, B; Bowcock Decl, ¶¶ 65-66, 72, Exs. B, C.

RESPONSE: Myriad objects to and disputes the characterization of the Abel and Anderson primer pairs as being used to amplify "intragenic marker D17S855" because the statement is vague as to what the maker is intragenic to, and from what date that allegation should be evaluated. Myriad further objects to the allegations of Paragraph 13 to the extent they implicate claim construction, rather than state facts.

14. Intragenic markers D17S855 and D17S932 became publicly available no later than July 12, 1993. Both markers are part of the *BRCA1* gene. Gregory Decl., ¶¶ 76-79, 86-88, Exs. A, B, C; Bowcock Decl., ¶¶ 66, 80-82, Exs. B, G, K.

RESPONSE: Myriad objects to and disputes the characterization of the markers D17S855 and D17S932 as "intragenic" because the sentence is vague as to what the makers are intragenic to, and from what date that allegation should be evaluated. Myriad additionally disputes the alleged dates when the markers became publicly available. Myriad further disputes the second sentence because it does not provide a date from which to evaluate the assertion that both markers are part of the BRCA1 gene. Myriad further objects to these allegations to the extent they implicate claim construction, rather than state facts.

15. Bowcock (1993) describes the steps and techniques researchers in the field would use to identify the sequence of *BRCA1*. Each step adopts conventional approaches that were

known in the field. Gregory Decl., ¶¶ 122-124, Ex. G; Bowcock Decl., ¶¶ 30-31, 34, 37-39, 42-45, 48, 52-53, Ex. G.

RESPONSE: Myriad objects to and disputes these statements as vague and because they do not identify any specific steps and techniques or conventional approaches, nor define the purported "field."

16. Genetic screening, such as screening the ΔF508 mutation for cystic fibrosis, was widely used by 1994. Gregory Decl., ¶ 104; Bowcock Decl., ¶ 61.

RESPONSE: Myriad objects to and disputes this statement as vague, including the use of the terms "genetic screening" and "widely used."

17. Miki (1994) discloses the identification of neutral sequence variations in BRCA1 that are not associated with breast or ovarian cancer (Table 3), as well as sequence variations that do cause a pre-disposition to breast or ovarian cancer (Table 2). Gregory Decl., ¶¶ 138, 167, Ex. AA; Bowcock Decl., ¶¶ 114-115, Ex. H.

RESPONSE: Myriad admits that Table 2 of Miki (1994) lists "[p]redisposing mutations in BRCA1," and that Table 3 of Miki (1994) lists "[n]eutral polymorphisms in BRCA1." Myriad objects to and disputes the remaining characterizations of Miki (1994) in Paragraph 17.

18. Friedman (1994) discloses the identification of neutral sequence variations in BRCA1 that are not associated with breast or ovarian cancer (Table 3), as well as sequence variations that do cause a pre-disposition to breast or ovarian cancer (Tables 2a and 2b). Gregory Decl., ¶¶ 147, 175, Ex. BB; Bowcock Decl., ¶¶ 118-119, Ex. L.

RESPONSE: Myriad admits that Table 3 of Friedman (1994) lists "[n]eutral polymorphisms in BRCA1"; that Table 2a of Friedman (1994) lists "[g]ermline mutations cosegregating with breast and ovarian cancer in BRCA1-linked families"; and that Table 2b of

Friedman (1994) lists "[s]ites, ages at diagnosis and laterality of cancers associated with BRCA1 mutations." Myriad objects to and disputes the remaining characterizations of Friedman (1994) in Paragraph 18.

19. U.S. Patent No. 5,747,282 discloses the identification of neutral sequence variations in BRCA1 that are not associated with breast or ovarian cancer, as well as sequence variations that do cause a pre-disposition to breast or ovarian cancer (Tables 11). Gregory Decl., ¶¶ 155, 183-184; Bowcock Decl., ¶ 120.

RESPONSE: Myriad admits that Table 11 of the '282 patent lists "Predisposing Mutations." Myriad objects to and disputes the remaining characterizations of the '282 patent in Paragraph 19.

20. Schutte (Oct. 1995) discloses two pairs of PCR primers derived from human chromosome 13. The primer pairs were used to amplify intragenic markers 886sl86 (91 base pairs) and 886s239 (76 base pairs), located within the *BRCA2* gene. Gregory Decl., ¶¶ 238-239, Ex. M.

RESPONSE: The second sentence does not provide a date from which to evaluate the allegation that the "primer pairs were used to amplify intragenic markers...located within the BRCA2 gene," and Myriad therefore disputes the allegations of the second sentence. Myriad further objects to the allegations of Paragraph 20 to the extent they implicate claim construction, rather than state facts.

21. "H47777" and "H48122" each is an EST sequence submitted to GenBank by RZPD Deutsches Ressourcenzentrum fuer Genomforschung GmbH, Inge Arlart on February 20, 1995. Both ESTs are located entirely within the *BRCA2* gene. Gregory Decl., ¶¶ 246-247, 256-257, Exs. EE, FF.

RESPONSE: Myriad disputes that H47777 and H48122 were submitted to the stated database on February 20, 1995. Myriad further disputes the second sentence because it is vague, and the sentence does not provide a date from which to evaluate the assessment that "[b]oth ESTs are located entirely within the BRCA2 gene." Myriad further objects to these allegations to the extent they implicate claim construction, rather than state facts.

22. Schutte (June 1995) compared normal (wild-type) DNA and tumor DNA, and discovered that the tumor DNA has a deletion in the *BRCA2* chromosomal region. Later it was confirmed that the deletion is within the *BRCA2* gene. Gregory Decl., ¶ 270, Ex. L.

RESPONSE: Myriad objects to and disputes the characterization of the Schutte (June 1995) article's disclosure in the first sentence of paragraph 22. Myriad lacks knowledge or information regarding the allegations of the second sentence of Paragraph 22, and accordingly disputes the same. Myriad further objects to these allegations to the extent they implicate claim construction, rather than state facts.

23. Three U.S.-based authors listed in Wooster (1995) reviewed and approved the manuscript before it was submitted to Nature on December 5, 1995. Gregory Decl., ¶¶ 274-275, Ex. Q.

RESPONSE: Myriad lacks knowledge or information regarding the allegations of Paragraph 23, and accordingly disputes the same.

24. Wooster (1994) mapped the *BRCA2* gene to a 6 centiMorgan region. It also discloses that the most likely region for *BRCA2* is between D13S260 and D13S267 (1 centiMorgan apart). Gregory Decl., ¶¶ 278-280, Ex. P.

RESPONSE: Myriad admits that the Wooster (1994) article attached as Exhibit P to the Gregory declaration states that "This analysis localized a second breast cancer susceptibility

locus, BRCA2, to a 6-centimorgan interval on chromosome 13q12-13." Myriad objects to and disputes the remaining allegations of the first sentence of Paragraph 24. Myriad objects to and disputes the characterization of Wooster (1994) in the second sentence of Paragraph 24. Myriad further objects to these allegations to the extent they implicate claim construction, rather than state facts.

25. A specific PAC contig that comprises the *BRCA2* gene, as well as the partial sequence of this contig, were released to the public domain no later than November 23, 1995. Gregory Decl., ¶ 288, Ex. K.

RESPONSE: Myriad objects to this statement as vague, and therefore disputes the allegations of Paragraph 25. Myriad additionally disputes the alleged date by which the "specific PAC contig" was released to the public domain. Myriad further objects to these allegations to the extent they implicate claim construction, rather than state facts.

26. PAC clones that contain the *BRCA2* gene, or fragments of the *BRCA2* gene, were available no later than February 1994. Gregory Decl., ¶ 291.

RESPONSE: Myriad objects to this statement as vague and also lacks knowledge or information regarding these uncorroborated allegations, and therefore disputes them. Myriad further objects to these allegations to the extent they implicate claim construction, rather than state facts.

27. All of the accused Ambry tests screen the same way for point mutations in BRCA1 and BRCA2. Elliott Decl., ¶ 6.

RESPONSE: Undisputed.

28. Ambry technicians use PCR to amplify all of the sequences of the exons of BRCA1 and BRCA2 as well as at least 20 nucleotides of the intronic sequences adjacent to each exon. *Id.* ¶ 8.

RESPONSE: Undisputed.

29. The primers used by Ambry to perform PCR contain sequences that are not derived or isolated from the sequences of human chromosomes 17q and/or 13. *Id.* ¶¶ 15-19.

RESPONSE: Undisputed.

30. The primers used by Ambry to sequence amplicons do not have any sequences derived or isolated from the sequences of human chromosomes 17q and/or 13. Id. ¶ 26.

RESPONSE: Undisputed.

31. Ambry aligns patient DNA sequences to the sequence for the whole human genome. *Id.* ¶¶ 32-34.

RESPONSE: Undisputed.

32. Ambry does not use allele specific probes to identify the presence of particular known variants. *Id.* ¶ 49.

RESPONSE: Myriad denies paragraph number 32, but notes that the paragraph is irrelevant because of the way that Ambry defines the term "allele specific probes." Ambry imposes its own definition onto that term to limit the term to "probes that detect a specific mutant" to then support its paragraph 32 statement that "Ambry does not use allele specific probes to identify the presence of particular known variants." Elliott Decl. at ¶ 49. However, that distinction is artificial and irrelevant because the patent claim at issue encompasses probes designed or specific for "normal" or wild-type BRCA "alleles" (*see, e.g.*,'441 patent at col. 19,

lines 24-30), and Ambry admits that it uses such normal or wild-type probes. Elliott Decl. at ¶ 49.

33. Gene by Gene technicians intend to use PCR to amplify all of the sequences of the exons of BRCA1 and BRCA2 as well as 50 nucleotides of the intronic sequence flanking each exon. Mittelman Decl., ¶ 16.

RESPONSE: Undisputed.

34. The primers Gene by Gene intends to use to perform PCR contain sequences that are not derived or isolated from the sequence of human chromosomes 17q and/or 13. *Id.*

RESPONSE: Undisputed.

35. Gene by Gene intends to align patient DNA sequences to the sequence of the whole human genome. *Id.* ¶ 20.

RESPONSE: Undisputed.

36. Gene by Gene does not intend to use allele-specific primers. *Id.* ¶ 21.

RESPONSE: Myriad denies paragraph number 36, but notes that the paragraph is irrelevant because of the way that Gene By Gene defines the term "allele specific probes." Gene By Gene appears to impose, like Ambry in paragraph number 32 above, the same definition onto that term to limit the term to "probes that detect a specific mutant" to then support its paragraph 36 statement that "Gene by Gene does not intend to use allele-specific primers." Mittelman Decl. at ¶ 21. However, that distinction is artificial and irrelevant because the patent claim at issue encompasses probes designed or specific for "normal" or wild-type BRCA "alleles" ('441 patent at col. 19, lines 24-30), and Gene By Gene admits that it uses such normal or wild-type probes. Mittelman Decl. at ¶ 21.

37. Monetary damages for price erosion and market loss can be calculated using accepted and customary financial accounting methods. Hampton Decl., ¶¶ 31, 40, 49.

RESPONSE: Disputed. *See* Declaration of James Kearl, Ph.D., ("Kearl Decl."), at 12-18.

38. On August 13, 2013, Myriad forecast 14% to 18% revenue growth for its core test products, including BRCA 1/2 tests, in Fiscal Year 2014. The forecast takes into consideration the recent emergence of competition for the BRCA 1/2 tests and also is in line with Myriad's May 2013 forecast, prior to Defendants entry in the BRCA 1/2 market. *Id.* ¶¶ 52-53, Ex. R.

RESPONSE: Undisputed, but irrelevant. *See* Kearl Decl. at 15.

39. Myriad currently holds over $400 million of cash and cash equivalents. *Id.* ¶ 66, Ex. U.

RESPONSE: Undisputed, but irrelevant. *See* Kearl Decl. at 10.

40. Myriad sets prices for its BRCA 1/2 tests through contracts with insurers. Ford 2nd Decl., ¶ 4. Customarily, prices set by such insurance contracts do not change frequently or quickly. Hampton Decl., ¶ 28.

RESPONSE: Undisputed as to the first sentence. Myriad disputes the characterization of the second sentence, which is in any event irrelevant. *See* Kearl Decl. at 12.

41. Myriad has licensed one or more of the patents-in-suit. Second Declaration of Alexander Ford ("Ford 2nd Decl."), Dkt. #27, ¶ 6.

RESPONSE: Undisputed. As Mr. Ford states, LabCorp received a license in 2002 which was limited in scope. Ford 2nd Decl., ¶ 6.

42. Following the Supreme Court's June 13, 2013 *Myriad* decision, the University of Washington Department of Laboratory Medicine, GeneDX Inc., Quest Diagnostics Inc., Pathway

Genomics Inc., and Ethigen, LLC began offering or announced they will offer BRCA 1/2 testing. Plaintiffs have not sued any of these entities for patent infringement. Hampton Decl., ¶ 30.

RESPONSE: In response to the first sentence of Paragraph 42, it is undisputed that certain of those entities began offering BRCA 1/2 testing after the June 13, 2013 decision, and that certain of those entities indicated that they intended to do so. The second sentence is undisputed, but Myriad denies any implication that bringing suit against such entities is in any way a prerequisite to relief.

43. If enjoined, Ambry and Gene by Gene will lose their headstart advantage of being first entrants in the market to offer an alternative BRCA 1/2 test to Myriad. *Id*. ¶ 58.

RESPONSE: Disputed. *See infra* at Section II(B).

44. Ambry invested an estimated $46.7 million in capital resources to be positioned to offer the first comprehensive multi-gene hereditary test for breast and ovarian cancer. Ambry expanded its laboratory and hired 110 additional employees. If enjoined, Ambry expects it will go out of business and layoff most or all of its 180 employees. *Id*. ¶ 57.

RESPONSE: Myriad lacks knowledge or information regarding the allegations of Paragraph 44, and accordingly disputes the same. *See infra* at Section II(B).

45. Breast and ovarian cancers are deadly diseases affecting a large number of women. Early risk detection of these cancers through BRCA 1/2 testing saves lives by assisting with diagnosis, preventative measures, and treatment. Swisher Decl., ¶¶ 19-20.

RESPONSE: Undisputed.

46. Many patients who want BRCA 1/2 testing cannot afford Myriad's BRCA 1/2 test price of $4,040. Swisher Dec., ¶¶ 122-24; Chao Decl., ¶¶ 26-28; Gaed Decl., Ex. H (Raker Decl., ¶¶ 6-10), Ex. I (Thomason Decl., ¶¶ 6-9). Ambry offers a multi-gene panel test including

BRCA 1/2 for $2,200. Gene by Gene offers its BRCA 1/2 test for $995. Chao Decl., ¶ 26; Mittleman Decl., ¶ 14. Patients who could not afford or whose insurance did not cover Myriad's BRCA 1/2 test have not been tested by Ambry. Matloff Decl., ¶ 10.

RESPONSE: Myriad disputes the first sentence of Paragraph 46. Ford 2nd Decl., ¶¶ 2-5. The second and third sentences are undisputed. Myriad lacks knowledge or information regarding the allegations of the last sentence, and accordingly disputes the same.

47. Myriad cannot offer second opinion testing of its own BRCA 1/2 tests. Swisher Decl., ¶ 121.

RESPONSE: Disputed in part. While Myriad does not offer its own second opinion testing (which would seem in any event to obviate the purpose of a second opinion), it does not and has not asserted its patents against others performing such testing. Ford 2nd Decl., ¶ 6.

48. Ambry currently provides hereditary cancer tests that include testing of BRCA 1 and BRCA 2 and offer features not available for Myriad's BRCA 1/2 test offerings, including test results reports containing the bases for variant classifications, both full sequencing and large rearrangement testing billed for one price under one insurance code, testing under health plans that currently do not cover Myriad testing, and multi-gene breast and ovarian cancer panel tests. Chao Decl., ¶ 16-21, 29, 50-51.

RESPONSE: Myriad lacks knowledge or information sufficient to admit or deny Dr. Chao's conclusory statement that "there are some payors as to which Ambry is in network and Myriad is not," because she does not identify them such that Myriad can assess the accuracy of her statement. Myriad does not dispute the remaining allegations of Paragraph 48, but they are irrelevant for the reasons set forth in Section II(C), *infra*.

49. Myriad's BRCA 1/2 tests do not automatically include large rearrangements, which are known to account for about 10% of all deleterious mutations. Swisher Decl., ¶¶ 63, 70-98. Ambry's BRCA 1/2 tests automatically include large rearrangements. Chao Decl., ¶ 17. Without large rearrangements, patients will receive false negatives. Swisher Decl., ¶¶ 72-82, 95-96; Morris Decl., ¶ 7; Matloff Decl. ¶ 7; Ledbetter Decl., ¶¶ 15-17, 20.

RESPONSE: Myriad does not dispute the second sentence of Paragraph 49, but the allegation is irrelevant. The remaining allegations and implications are disputed. Declaration of Larry J. Geier, M.D. ("Geier Decl."), ¶¶ 36-37. *See also* Declaration of Jennifer J. Tittensor, M.D., FACS ("Tittensor Decl."), ¶ 6.

50. Comprehensive public databases of BRCA 1/2 data allow genetic testing laboratories and researchers to better understand and classify more variants with more reliability, thereby advancing patient care. Nussbaum Decl., ¶¶ 27-40; Ledbetter Decl., ¶¶ 35-44; Swisher Decl., ¶¶ 26-32. Myriad does not share BRCA 1/2 data with public databases. Ledbetter Decl., ¶¶ 36-40. Ambry and Gene by Gene have committed to sharing BRCA 1/2 data with public databases, and Ambry has already begun doing so. Chao Decl., ¶ 64; Mittelman Decl., ¶¶ 25-26.

RESPONSE: Myriad disputes the first sentence of Paragraph 50. Declaration of Julie Eggington, Ph.D. ("Eggington Decl."), ¶¶ 13; 16-21. Myriad does not dispute the second sentence of Paragraph 50, but denies any related implication. *Id*. Myriad lacks knowledge or information sufficient to admit or deny the third sentence of Paragraph 50.

51. In 1996, Myriad established a public database to collect and organize data and personal and family cancer histories for persons tested for mutations in *BRCA 1* and *BRCA 2*. Nussbaum Decl., ¶ 17.

RESPONSE: Undisputed.

52. In 2004, Myriad made its last major deposit to the public database, and in 2005 Myriad stated its intention of keeping as a trade secret patient sequence data. Nussbaum Decl., ¶ 21.

RESPONSE: Disputed in part. Eggington Decl., ¶¶ 12-14.

53. The lack of comprehensive, publicly available databases of patient sequence variants is one of the most critical problems facing clinical geneticists and their patients today. Nussbaum Decl., ¶ 27.

RESPONSE: Disputed. Eggington Decl., ¶¶ 17-21.

54. Ambry's VUS rate (*i.e.*, how often a variant is classified as a variant of unknown significance) is presently 4.5%. Chao Decl., ¶¶ 52-53. Gene by Gene estimates an initial VUS rate less than 12-13%. Mittleman Decl., ¶ 28. Myriad reports a 3% VUS rate but, unlike Ambry, does not disclose the internal data upon which it relies to make its classifications, so Myriad's VUS rate is unverifiable. Swisher Decl., ¶¶ 43-49; Chao Decl., ¶¶ 59-60.

RESPONSE: Disputed. Eggington Decl., ¶¶ 6-9; Declaration of Larry J. Geier, M.D. ("Geier Decl."), ¶¶ 39, 29.

55. Ambry's analytic sensitivity is greater than 99%, with a false negative rate much less than 0.1%. Ambry's false positive rate is virtually 0% because Ambry confirms any variant it finds by next-gen sequencing with a second Sanger sequencing test. Myriad does not report the analytical sensitivity of BRACAnalysis or BART. Chao Decl., ¶¶ 37, 41, 42; Swisher Decl., ¶¶ 63, 65.

RESPONSE: Disputed. Declaration of Alexander Ford ("Ford Decl."), Dkt. # 6, ¶ 17; *see* Geier Decl., ¶ 29; Plf's Ambry Mot. at 37.

56. Myriad announced this year that it intends to offer a new multi-gene panel test where it will switch to next-generation sequencing, a sequencing method Ambry has long used in its tests but Myriad has not used. If implemented, Myriad's new myRisk panel test will be nearly identical to Ambry's CancerNext test, including using the same third party, RainDance Technologies, Inc., to aid in the design of primers. Chao Decl., ¶¶ 45-47.

RESPONSE: Myriad does not dispute that it intends to offer a new multi-gene panel test known as myRisk Hereditary Cancer™ panel. Myriad disputes the characterization that the test will be "nearly identical" to that of Ambry, as the myRisk Hereditary Cancer™ panel was in development since well before this lawsuit. *See* Ford Decl., ¶ 23.

57. Myriad has asserted its patents to block scientific research, collaborative data collection and sharing, patient screenings at cancer diagnostic facilities, and development and offering of additional, alternative, and more affordable technologies. Stiglitz Decl., ¶¶ 23-40; Leonard Decl., ¶¶ 26-44; Ledbetter Decl., ¶¶ 11-21, 35-47; Matloff Decl., ¶¶ 6-7; Gaede Decl. Ex. B (Ganguly Decl., ¶¶ 3-14), Ex. E (Kazazian Decl., ¶¶ 3-11), Ex. F (Ostrer Decl., ¶¶ 5-12).

RESPONSE: The allegations in Paragraph 57 are irrelevant to any issue presented by Myriad's Motion, for the reasons set forth in Myriad's Objections to Evidence filed concurrently herewith. The allegations are also disputed. *See* Geier Decl., 21-23; 42; Discussion at Section II(C)(2), *infra*.

58. A 2001 survey of laboratory directors throughout the United States conducted through a grant from the National Human Genome Research Institute of the National Institutes of Health showed that "patents on genes used for clinical diagnostics inhibit the conduct of research to further the development of improvements to genetic tests [and] . . . inhibit clinical diagnostic laboratories from providing clinical tests and services. The survey further showed such "patents

are not necessary to incent either the research on initial discoveries or the development of clinical applications and commercializable products." Cho Decl., ¶¶ 24-25.

RESPONSE: The allegations in Paragraph 58 are irrelevant to any issue presented by Myriad's Motion, for the reasons set forth in Myriad's Objections to Evidence filed concurrently herewith. Furthermore, Myriad disputes the proposition that patents pertaining to genetic innnovations "inhibit research" or "the development of clinical applications and commercializable products." *See* Declaration of David G. Mangum ("Mangum Decl."), Exh. E (Brief of Drs. Larry Geier, William Harb, Adam Ofer, and Donald Aptekar as Amici Curiae in Support of Respondents); Exh. F (Brief for the Philadelphia Intellectual Property Law Association as Amicus Curiae in Support of Respondent Myriad Genetics, Inc.).

ARGUMENT

I. MYRIAD IS LIKELY TO PREVAIL ON THE MERITS OF ITS PATENT INFRINGEMENT CLAIMS.

A. The Legal Standards Applicable to Myriad's Motion.

Generally, the parties do not disagree regarding the standard governing a motion for preliminary injunctive relief. *Compare* Plfs' Ambry Mot. at 8-9; Plfs' GBG Mot. at 8-9 with Defs' Opp. at 22-24. However, two points bear clarification. First, in order to warrant entry of a preliminary injunction, the Court need only conclude that Myriad is likely to prevail on the merits with respect to ***at least one*** of the asserted claims (assuming the remaining factors are established). *Astrazeneca LP v. Apotex, Inc*., 633 F.3d 1042, 1050 (Fed. Cir. 2010), *r'hg denied* ("For a patentee to establish that it is likely to succeed on the merits, it 'must demonstrate that it will likely prove infringement of ***one or more claims*** of the patents-in-suit, and that ***at least one of those same allegedly infringed claims*** will also likely withstand the validity challenges presented by the accused infringer.'") (emphasis added). Second, any implication that the Federal Circuit's holding in *Aria Diagnostics, Inc. v. Sequenom, Inc.*, -- F.3d --, 2013 WL 4033479 (N.D. Cal. July 5, 2012), permits the Court to disregard consideration of the equitable factors if it finds a substantial question of validity or infringement is incorrect. In *Aria Diagnostics*, the district court found substantial questions on infringement and validity, and accordingly "only briefly addressed the traditional factors." *Id*. at * 6. The Federal Circuit ruled that the district court "erred in some aspects of its brief analysis," and vacated and remanded the case for further proceedings before the district court. *Id*.[7]

[7] Furthermore, two assertions in Defendants' Opposition regarding Myriad's opening brief similarly bear correction. First, Defendants are incorrect in stating that Myriad implied "that the Court may issue a preliminary injunction even where some factors favor Defendants." Defs' Opp. at 22, n.2. In fact, Myriad correctly stated that "[n]o one element is dispositive." The district court must weigh and measure each factor against the other factors and against the form

B. Every Claim Asserted by Myriad Meets the Standard for Patent Eligibility Set Forth in the United States Supreme Court's *AMP* and *Mayo* Decisions.

As set forth in Myriad's motion, the Supreme Court in *AMP* issued a narrow ruling that pertains to a small fraction of Myriad's overall patent estate of 24 patents with 520 claims. With regard to composition of matter claims, the Court, rather than entering the sweeping holding Defendants urge, altered prior precedent (which had broadly allowed the patenting of any DNA molecule so long as it was at least extracted from its natural surroundings) in only one limited respect. Specifically, it held that a handful of Myriad's patent claims (none of which are at issue in this case), encompassing "a naturally occurring DNA segment" that is "extract[ed]" "from [human] cells," were patent-ineligible "products of nature." *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S.Ct. 2107, 2111, 2112 (2013) ("*AMP*"). The scope and limited extent of the Court's decision is set forth in the final sentence of its opinion: "We ***merely hold*** that genes and the information they encode are not patent eligible under §101 ***simply because*** they have been isolated form the surrounding genetic material." *Id*. at 2120 (emphasis added). However, the Court also held that other Myriad claims—those limited to synthetic DNA, and specifically cDNA—did "not present the same obstacles to patentability" because "the lab technician unquestionably creates something new when cDNA is made." *Id*. at 2119.

Further, the Court went out of its way to reaffirm the patentability of methods applying genetic discoveries. In "hold[ing] that genes and the information they encode are not patent eligible under § 101 simply because they have been isolated from the surrounding genetic material" (*id.* at 2120), the Court reaffirmed that "[a]s the first party with knowledge of the

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and magnitude of the relief requested. Plfs' Ambry Mot. at 8; Plfs' GBG Mot. at 8. Second, with respect to applicable choice of law, Myriad correctly stated that "[p]rocedural issues, such as compliance with Rule 65, are governed by regional authority." Plfs' Ambry Mot. at 8, n.3; Plfs' GBG Mot. at 8, n.3. Defendants state nothing to the contrary.

[BRCA1 and BRCA2] sequences, Myriad was in an excellent position to claim applications of that knowledge", and that "[m]any of its unchallenged claims are limited to such applications." *Id.*

Myriad has asserted both composition of matter and method claims in seeking a preliminary injunction. Thus, there are two core questions for this Court to address regarding patentability of the asserted claims: (1) whether Myriad's primer pair claims pertain to "naturally occurring DNA segments," or ***synthetic molecules*** created by man in the laboratory; and (2) whether Myriad's method claims are directed to a law of nature, or to an ***application*** of a law of nature. As set forth below, the analytical construct applied by the Supreme Court compels the conclusion that every claim asserted by Myriad—whether pertaining to a composition of matter or to a method of applying Myriad's discoveries about the BRCA1 and BRCA2 genes—is patentable. Defendants' arguments to the contrary rest not on the language of the Court's *AMP* and *Mayo* decisions, but on a forced and overly broad construction that cannot be supported by the language in those decisions.

Indeed, one struggles under Defendants' arguments to find anything patentable Myriad could have claimed in the wake of its groundbreaking discovery of the sequence of the BRCA1 and BRCA2 genes. The Supreme Court was acutely sensitive to this issue in *AMP*, as demonstrated in the narrowness of its decision that only naturally occurring DNA extracted from a human cell is patent ineligible, as well as the Court's generalized approval of method claims applying genetic discoveries (and the specific statement that Myriad, in particular, was in an excellent position to claim applications of its BRCA gene discoveries).

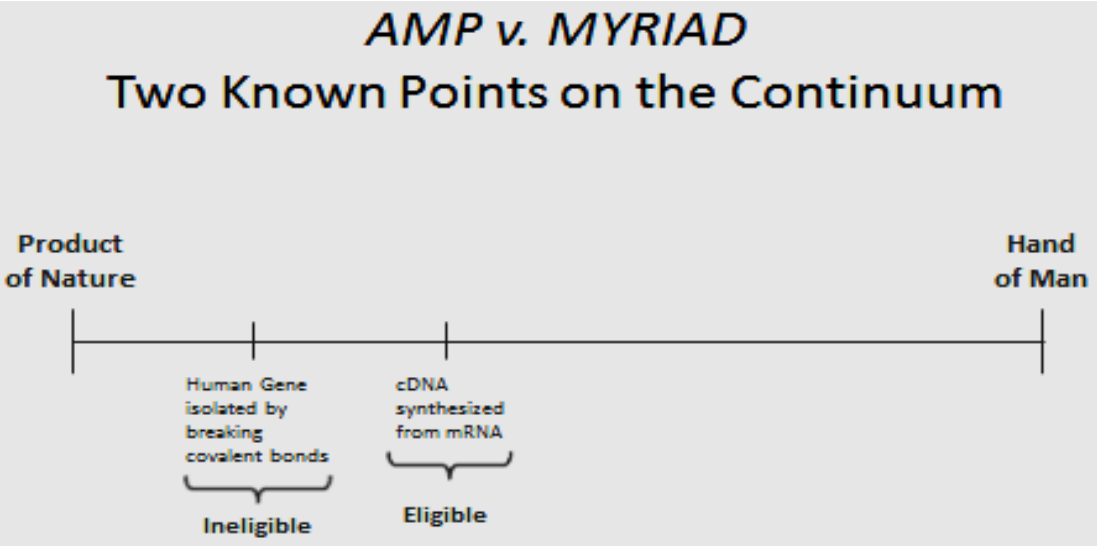
1. The Supreme Court in *AMP* Established a Continuum Which It Applied to Conclude that Claims Pertaining to Genomic DNA Are Not Patentable, While Claims Pertaining to Synthetic DNA Are Patentable.

The parties' dispute regarding the patentability of the claims at issue here turns upon two vastly different views of the nature and scope of the Supreme Court's holding. As a result, it is worth setting aside characterizations of that holding, and instead engage in a careful examination of the language of the decision itself.

To that end, the Supreme Court expressly framed the holdings that it made as addressing only two issues. With respect to the first issue, it stated: "[t]his case … requires us to resolve whether a naturally occurring segment of … DNA[] is patent eligible under 35 U.S.C. § 101 ***by virtue of its isolation from the rest of the human genome***." *AMP*, 133 S.Ct. at 2111 (emphasis added). Then, as to the second issue, it stated "[w]e also address the patent eligibility ***of synthetically created DNA known as complementary DNA (cDNA), which contains the same protein-coding information found in a segment of natural DNA*** but omits portions within the DNA segment that do not code for proteins." *Id.* (emphasis added). Thus, in the very phrasing of the issues, the Court emphasized that the determination of patent eligibility turned not on whether the composition of matter "contain[ed] the same protein-coding information" as DNA found in nature, but rather how that DNA molecule was made—either a product of nature merely "isolate[ed] from the rest of the human genome" or a "synthetically created" product of human ingenuity and design.

In ultimately concluding that the answer to question one is "not patentable," and the answer to question two is "patentable," the Supreme Court established a continuum having at one end a product of nature and, at the other end, a product created by human invention. The Supreme Court concluded that isolated naturally occurring DNA segments fall to the "product of

nature" side of the continuum, while cDNA involved enough of the hand of man to be patent eligible. "[A] naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated." *Id*. at 2111. cDNA, however, "is patent eligible because it is not naturally occurring. We, therefore, affirm in part and reverse in part the decision of the United States Court of Appeals for the Federal Circuit." *Id*.



Naturally occurring genes and cDNA thus constitute two known points on the "product of nature" v. "hand of man" continuum erected by the Court. The Court instructs that naturally occurring DNA–"genes and the information they encode" are not patent eligible "***simply because they have been isolated*** from the surrounding genetic material." *Id*. at 2120 (emphasis added). cDNA, on the other hand, reflects a different point on the continuum because "the lab technician ***unquestionably creates something new*** when cDNA is made," and as such it "does not present the same obstacles to patentability as naturally occurring, isolated DNA segments." *Id*. at 2119 (emphasis added). Because cDNA is "distinct from the DNA from which it was derived," cDNA is "not a "product of nature" and is patent eligible under §101. *Id*.

The Supreme Court also identified examples of each type of claim from among Myriad's patent claims and referred to them as "representative claims." Claims 1 and 5 of the '282 patent

were identified as representative of claims to genomic DNA, with claim 1 covering the entire BRCA1 gene and claim 5 any segment thereof "having at least 15 nucleotides of the DNA of claim 1." The Court recognized that "the practical effect of claim 5 is to assert a patent on any series of 15 nucleotides that exist in the typical BRCA1 gene." *Id*. at 2113. Claims 2 and 6 of the '282 patent were identified as representative of the "cDNA" claims, with claim 2 covering the entire BRCA1 cDNA molecule and claim 6 any 15-nucleotide or larger segment thereof. The Court stated that claim 6 "operates similarly to claim 5, ***except that it references the cDNA-based claim 2***." *Id*. at 2113 (emphasis added).[8]

The language employed by the Supreme Court is important to understanding these points on the product of nature v. product of the hand of man continuum. In discussing naturally occurring DNA segments, the Court stated "[s]cientists can . . . ***extract DNA from cells*** using well known laboratory methods. These methods allow scientists ***to isolate specific segments of DNA—for instance, a particular gene or part of a gene***, which can then be further studied, manipulated, or used." *Id*. at 2112 (emphasis added). On the other hand, the Court noted that "[i]t is also possible ***to create DNA synthetically*** through processes similarly well known in the field of genetics. One such method begins with an mRNA molecule and uses the natural bonding properties of nucleotides to ***create a new, synthetic DNA molecule . . . This synthetic DNA created in a laboratory from mRNA is known as complementary DNA (cDNA)***." *Id*. (emphasis added).[9]

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[8] The Supreme Court already had noted that claim 2, claims DNA with "the nucleotide sequence set forth in SEQ ID NO:1" and that, "[i]mportantly, SEQ ID NO:1 lists only the cDNA exons in the BRCA1 gene, rather than a full DNA sequence containing both exons and introns." *Id*.

[9] The "natural bonding properties of nucleotides" the Supreme Court refers to are Watson-Crick chemical bonding (*i.e.*, A to T and C to G). By nonetheless finding these synthetic DNA

Moreover, in holding cDNA patentable, the Court expressly rejected the argument that nucleotide sequence similarity between naturally occurring DNA and cDNA requires a finding of unpatentability, holding that it "may be so" that "the nucleotide sequence of cDNA is dictated by nature, not by the lab technician," but "the lab technician unquestionably creates something new when cDNA is made. … As a result, cDNA is not a 'product of nature' and is patent eligible under § 101, except insofar as very short series of DNA may have no intervening introns to remove when creating cDNA." *Id.* at 2119. In that situation, the Court reasoned, but did not hold, that such a short strand of cDNA "***may be*** indistinguishable from natural DNA." *Id*. (emphasis added). No holding on that point was necessary because that situation was not presented.[10] Thus, it is not the nature of the nucleotide sequence that determines whether a particular DNA molecule is patentable, but rather the extent to which the molecule constitutes a "naturally occurring" compound versus one created in a laboratory. Indeed, in framing the issue, the Court expressly noted that cDNA shares the "same protein-coding information" with a segment of natural DNA from the same gene. *Id*. at 2111.

The full context of the words used by the Court emphasized this distinction between naturally occurring DNA—a product of nature—"extracted" or "isolated" from the body, and synthetic DNA "created" or "synthesized" in the laboratory—a product of the hand of man:

> Scientists can . . . ***extract*** DNA from cells using well known laboratory methods. These methods allow scientists to ***isolate*** specific segments of DNA—for instance, a particular gene or part of a gene—which can then be further studied, manipulated, or used. It is also possible to ***create*** DNA ***synthetically*** through processes similarly well known in the field of genetics. One such method begins with an mRNA molecule and uses the natural bonding properties of nucleotides to

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molecules patentable, the Court rejected any argument that any claim that applies these properties is, therefore, unpatentable.

[10] The only genes at issue here, BRCA1 and BRCA2, are long and complex with many exons and introns. As a result, BRCA1 and BRCA2 cDNA necessarily omits intervening introns.

> ***create a new, synthetic DNA molecule***. . . . This synthetic DNA created in the laboratory from mRNA is known as complementary DNA (cDNA).

Id. at 2112. That language also makes clear that the Court used the word "isolate" in its decision only to mean DNA "extract[ed]" from a human cell, and that the Court did not intend the word "isolate" to apply to anything else.

Indeed, the Court expressly made the same distinction later in its opinion, stating in reference to the representative genomic patent claims as contrasted to the cDNA-based claims that:

> Myriad's patents would, if valid, give it the exclusive right ***to isolate*** an individual's BRCA1 and BRCA2 genes (or any strand of 15 or more nucleotides within the genes) ***by breaking the covalent bonds that connect the DNA to the rest of the individual's genome***. The patents would also give Myriad the exclusive right ***to synthetically create BRCA cDNA***. …

Id. at 2113 (emphasis added). By this language the Court further emphasized that its use of the word "isolated" referred only to DNA "extracted" from a human cell "by breaking the covalent bonds that connect the DNA" to the genome, and did not apply to synthetic DNA. The same conclusion follows from the Court's characterization elsewhere of the Federal Circuit's opinion: "The central dispute among the panel members was whether the act of isolating DNA—separating a specific gene or sequence of nucleotides from the rest of the chromosome—is an inventive act that entitles the individual who first isolates it to a patent." *Id*. at 2114. Thus, the Supreme Court used the term "isolation" only to mean "extraction" of genomic DNA from human cells by "sever[ing] chemical bonds [between the genomic DNA and the remaining material in the cell]." *Id*. at 2118.[11]

[11] Rather than address the word "isolate" as used by the Supreme Court, Defendants instead revert to the district court's claim construction of a different term, "isolated DNA," not used by the Supreme Court and not at issue before the Court. Defs' Opp. at 26-33. That discussion is not pertinent here. Claim construction turns on how a term used in a patent claim would be understood by one of skill in the art in light of the patent specification. The Supreme Court in

The Court also articulated the policy considerations underlying the product of nature vs. product of the hand of man continuum: "Laws of nature, natural phenomena, and abstract ideas are not patentable. Rather, they are the basic tools of scientific or technological work that lie beyond the domain of patent protection. . . .[W]ithout this exception, there would be considerable danger that the grant of patents would tie up the use of such tools and thereby inhibit future innovation premised thereon." *Id*. at 2116 (citations omitted). At the other end of the continuum, however, "[t]he rule against patents on naturally occurring things is not without limits, . . . for all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas, and too broad an interpretation of this exclusionary principle could eviscerate patent law. *Id*. (citation omitted). The Supreme Court then balanced these two concerns and held that, while purely natural phenomena could not be patented, the mere fact that an invention may employ the laws of nature does not by itself render it unpatentable; indeed, it is difficult to conceive of a useful invention that does not employ such natural laws to some extent.

Moreover, the Supreme Court did not, as Defendants assert, limit its patentability holding to cDNA to the exclusion of other forms of synthetic DNA. To the contrary, it recognized that cDNA is merely one form of synthetic DNA, and at least implicitly recognized that other synthetically created DNA molecules are similarly patent eligible. Specifically, the Court

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AMP did not purport to define the claim term "isolated DNA," nor did it use the word "isolate" with particular reference to any patent claim. Rather, it used the word "isolate" synonymously with "extract."

For similar reasons, Defendants' reliance upon the district court's opinion (Defs' Opp. at 27-28) is misplaced. That decision provides no guidance to this Court. That court's holding that "isolated DNA"—referring in that case to both "DNA originating from the cell" and synthesized DNA—was unpatentable because both types of DNA share the identical nucleotide sequence as genomic DNA, was reversed by the Federal Circuit. The Supreme Court ultimately affirmed the Federal Circuit in part, holding only that genomic DNA extracted from the cell was unpatentable. The district court's ruling in that case thus is not pertinent here.

recognized that, in contrast to naturally occurring DNA that may be "extracted from cells using well known laboratory methods," "[i]t is also possible to create DNA synthetically through ***processes*** similarly well known in the field of genetics." *Id*. at 2112 (emphasis added). It went on to discuss in detail only "[o]ne such method" of creating synthetic DNA which "begins with an mRNA molecule and uses the natural bonding properties of nucleotides to create a new, synthetic DNA molecule. … This synthetic DNA created in the laboratory from mRNA is known as complementary DNA (cDNA)." *Id*. The Court discussed cDNA in detail because the only claims limited to a synthetic form of DNA before it were directed to cDNA. However, the Court expressly recognized that there are several ways of creating synthetic DNA of which the creation of cDNA was only "[o]ne such." The Court thus at least implicitly ruled that other forms of synthetic DNA are also patentable.[12]

However, even if the Court did not at least implicitly rule on all forms of synthetic DNA, a finding of patentability of the synthetic primer pairs at issue here nonetheless is required by its holding. This is because DNA synthesized in a laboratory as an application of knowledge of the BRCA sequence, such as the DNA primer pairs at issue here, are even further removed from naturally occurring, genomic DNA than is cDNA. To create cDNA in a laboratory, a lab technician uses mRNA—a naturally occurring molecule taken from a human cell—as a starting material and then mimics in a test tube the natural viral process of reverse transcription to produce cDNA copies of that mRNA. *Id.* at 2111-12; Pribnow Decl. at ¶ 78. Unlike cDNA, primers and probes are not made using a naturally occurring starting material (mRNA). In fact,

[12] This conclusion is mirrored in the Federal Circuit's opinion. It noted that, in contrast to genomic DNA that "can be extracted from its cellular environment using a number of well-established laboratory techniques," "DNA molecules can also be synthesized in the laboratory. ***One type*** of synthetic DNA molecule is complementary DNA [which] is synthesized from mRNA using complementary base pairing in a manner analogous to RNA transcription." 689 F.3d at 1313-14 (emphasis added).

as Defendants' declarant Dr. Pribnow admits, the primers at issue here are laboratory designed and engineered from scratch by technicians using biological tools. Pribnow Decl. at ¶ 91; Roa Decl. (Dkt. #63) at ¶¶ 6, 16. Because the claimed primers are synthetically created, and do not use any genomic DNA as a starting material, they logically must fall further along the continuum towards the hand of man than cDNA, and are patentable for the same reasons that the Court held cDNA to be patentable.[13]

2. Each of the Primer Pair Claims Asserted Here Are Patent-Eligible Under *AMP*.

The composition of matter claims asserted here—claims 16-17 of the '282 patent and claims 29-30 of the '492 patent—recite a "pair" of single-stranded DNA "primers" for determining BRCA1 and BRCA2 sequences through a polymerase chain reaction (PCR). Such primers are patent eligible under 35 U.S.C. § 101 based on the ruling in *AMP* because they (1) are not naturally occurring DNA extracted from human cells; (2) are a pair of synthetic DNA molecules, specially designed and made by the hand of man in a laboratory; and (3) are markedly distinct both in form and function from naturally occurring DNA. Indeed, even a single primer molecule would qualify as patent eligible under *AMP*. *A fortiori*, a functionally-coordinated ***pair*** of single-stranded DNA primers capable of synthesizing a new DNA molecule having a sequence in common with a specific portion of the sequence of BRCA1 or BRCA2 genes manifestly *does not occur in nature* and is patent eligible.

[13] The Amici also raise a First Amendment challenge to Myriad's claims. *See* Amici Opp. at 17-21. This argument fails because it is the very same argument Amicus ACLU argued on behalf of the Petitioners before the Supreme Court, right down to their "carburetor" analogy. Brief for Petitioners at 55-58 (Jan. 23, 2013). The ACLU similarly presented this argument to the Federal Circuit. Brief of Appellees at 60-63 (Nov. 30, 2010). Both the Federal Circuit and Supreme Court declined to find any First Amendment issue, and the Amici have not advanced any reason for this Court to deviate from those rulings.

a. The Claimed Primers are Patent Eligible Because They Are Synthetic Compositions that Fall Squarely Within *AMP*.

Defendants' declarant Dr. Pribnow agrees that the claimed primer pairs are "synthesized in a laboratory rather than in the body." Pribnow Decl. at ¶ 91. Defendants also cite to declarations filed in the *AMP* case to support the fact that primers are "short chemically-synthesized" molecules. *See* Defs' Opp. at 33-37 (and citations to Kay Decl. attached as Exhibit D to the Gaede Decl. filed in this case).[14]

Accordingly, the claimed primer pairs do not fall within the ambit of what the Supreme Court held unpatentable in *AMP*. Specifically, they are not "a naturally occurring segment of" DNA that has merely been "extract[ed]" "from [human] cells" "by breaking the covalent bonds that connect the DNA to the rest of the individual's genome" and, in that manner, "isolat[ed] from the rest of the human genome" and "surrounding genetic material." *AMP*, 133 S.Ct. at 2111, 2112, 2113, 2120. To the contrary, they are synthetic DNA molecules created in the laboratory, and specially designed to work together to prime a particular polymerase chain reaction targeted at a segment of the BRCA1 or BRCA2 gene.

The term "synthetic" is substantive, not semantic. It refers to the claimed composition's *origin*, which is what the Court emphasized in its holding. Some of Myriad's claims in *AMP* were held invalid because some of the compositions encompassed by those claims *originated* in the human body, and the sole basis for claiming them was merely separating them from their natural origins by breaking of covalent bonds. cDNA and primers are fundamentally different because they originate not in the human body, but in a laboratory. In fact, primers originate in

[14] Indeed, the '282 patent and '492 patent specifications describe primers as being "***synthesized*** using techniques which are well known in the art. Generally, the ***primers can be made using oligonucleotide synthesizing machines*** which are commercially available." '282 patent at col. 16, lines 42-46; '492 patent at col. 15, lines 29-33 (emphasis added for both).

the head of the scientist designing them. To be sure, the scientist utilizes his knowledge of the genetic sequences, chemistry, and the complementarity of DNA bases in designing a particular pair of primers, just as any inventor makes use of natural laws and natural building blocks in creating any invention. For example, a researcher creating a new pharmaceutical molecule will design it to be complementary to bind to a receptor within the body based on natural laws and building blocks. But when a scientist designs a pair of primers and imbues them with the coordinated chemical properties needed to carry out a specific chemical reaction, the scientist performs the hallmark of "invention" in that he literally *conceives* of brand new molecules. Their genesis is not in extracting a pre-existing natural molecule from its surroundings, but instead in reducing this conceived idea to practice by building ("synthesizing") a completely new molecule where none existed before.

b. <u>The Claimed Primers are Patent Eligible Because They Are Distinct From Naturally Occurring DNA, and Possess a Utility Not Found in Such DNA.</u>

The claimed primer pairs are patentable for the additional reason that they are "distinct" from naturally occurring DNA. As noted above, in ruling that cDNA is patent eligible, the Supreme Court held that although the "nucleotide sequence of cDNA is dictated by nature," that fact does not matter because cDNA is "distinct" from naturally occurring DNA. Although cDNA shares its nucleotide sequence with portions of the native gene, the distinctions emphasized by the Court were that cDNA is synthesized in a laboratory and cDNA contains only the exons from the gene with the non-coding introns removed. *AMP*, 133 S.Ct. at 2112, 2119. The logical conclusion from that ruling is that any synthetic DNA molecule that is distinct from

naturally occurring DNA is patent eligible, regardless of whether its nucleotide sequence may be "dictated by" the natural DNA.[15]

Here, the claims at issue all require a "pair of single-stranded primers." A functionally-matched ***pair*** of single-stranded DNA molecules capable of synthesizing a new DNA molecule having a sequence in common with a specific portion of the sequence of BRCA1 or BRCA2 genes does not occur in nature. Primers used in a polymerase chain reaction are designed and used ***in pairs***. The design of one primer in the pair profoundly influences that of the other so they can work together and their combined, complementary chemical properties can catalyze a chemical reaction to synthesize a specific DNA molecule of interest (an amplicon). Roa Decl. ¶¶ 6-12. Defendants do not and cannot point to a natural equivalent of a pair of short disparate single strands of DNA, especially a pair that can work in conjunction with each other to synthesize a DNA molecule having a specific sequence of interest. *See* Defs' Opp. at 9-10, 25-37; Pribnow Decl. at ¶¶ 14-114.

While a single primer is patent eligible in and of itself because it is a synthetic, not a natural, molecule; *a fortiori*, a specific ***pair*** of primers that operate together to result in the synthesis of a new DNA molecule with a specific chemical structure is patent eligible. While a single primer is already not a product of nature, a pair of primer molecules with carefully

[15] The Federal Circuit found cDNA patentable for similar reasons. The majority opinion held that "the claimed cDNAs are especially distinctive [from naturally occurring DNA], lacking the noncoding introns present in naturally occurring chromosomal DNA. They are ***even more the result of human intervention into nature [than merely isolated genomic DNA]*** and are hence patent-eligible subject matter." *Association for Molecular Pathology v. United States Patent & Trademark Office*, 689 F.3d 1303, 1329 (Fed. Cir. 2012), *aff'd in part, rev'd in part*, 133 S.Ct. 2107 (2013) (emphasis added). The concurring opinion added that cDNA is patentable because they "are the creation of man, made using biological tools." *Id.* at 1341 (Moore, J., concurring in part). Although "the claimed isolated cDNA is inspired by nature," and by natural RNA in particular, it "has a different chemical structure from RNA." *Id.* Even in partial dissent, Judge Bryson agreed that the cDNA claims were "eligible for patenting" because cDNA is "created in the laboratory" and is "human-made."

designed and ***matched*** chemical properties is even further removed from being a product of nature.[16] Defendants' argument to the contrary would make any collection of elements ineligible for patenting simply because the individual elements are based on natural products or are designed to be complementary to a naturally occurring molecule. Based on that approach, it is difficult to imagine what would be eligible for patenting because, as the Supreme Court noted, "all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas," and "too broad an interpretation of this exclusionary principle could eviscerate patent law." *AMP*, 133 S.Ct. at 2116.

Moreover, each member of the primer pair is markedly "distinct" from naturally occurring genomic DNA in a number of ways. Each primer is a relatively short molecule (typically from 15 or 18 nucleotides long up to 25 or 30 nucleotides long). *See* Roa Decl. at ¶¶ 22, 14, 31; Pribnow Decl. at ¶ 91. In contrast, the naturally occurring genomic DNA in each of the BRCA1 and BRCA2 genes is a series of 80,000 nucleotides. *Id.* at ¶ 14; *AMP*, 133 S.Ct. at 2112. This distinction goes far beyond "size," however, as it renders the very chemical structure and chemical properties of the molecules dissimilar.

Nor does this distinction reflect the incidental chemical differences between the chromosome in its natural environment and an entire BRCA1 gene extracted from the chromosome, which the Supreme Court found insufficient to constitute invention. An extracted

[16] This conclusion is further buttressed by the added unlikelihood of a pair of matched primers spontaneously occurring in nature. On a related concept, the *AMP* Court recognized but dismissed as irrelevant to patentability the possibility that a rare, random process such as viral infection could conceivably yield a genomic DNA region that would have an identical sequence to a cDNA (e.g., pseudogenes). *AMP*, 133 S.Ct. at 2119, n. 8. The same concept applies with more force to a single primer and even more to a *pair* of primers, where the notion of a pair of DNA molecules each of just the right size and with the precise pairing of sequences (not overlapping, not too far apart, not hybridizing to the same strand, etc.) existing in the same vicinity in nature is a statistical impossibility.

BRCA1 gene retains most of the properties of the native gene and, as emphasized by the *AMP* Court, Myriad's patent claims did not rely on or recite any of the properties gained through extraction. *AMP*, 133 S.Ct. at 2118 ("Myriad's claims are simply not expressed in terms of chemical composition, *nor do they rely in any way on the chemical changes that result from the isolation of a particular section of DNA.* Instead, the claims understandably focus on the genetic information encoded in the BRCA1 and BRCA2 genes.") (Emphasis added). Rather than Myriad dictating such new properties, Judge Bryson noted that "[t]he only material change made to those genes from their natural state is the change that is *necessarily incidental* to the extraction of the genes from the environment in which they are found in nature." 689 F.3d 1303, 1350. In contrast, the primer pair claims at issue here are specifically limited according to the chemical properties designed and built into the pair of primers by the scientist, and not attainable in any naturally occurring molecule(s); specifically, the ability to prime a chemical reaction that "results in the synthesis of DNA having all or part of the sequence of the BRCA1 gene."

The claimed primers are distinct for the additional reason that they have utilities, *explicitly recited in the claims,* that are not present in naturally occurring DNA and not even present in cDNA. The Federal Circuit held in its *AMP* decision that such utilities render a DNA molecule distinctive. Judge Moore noted that cDNA "have a distinctive character and use, with markedly different chemical characteristics from either the naturally occurring RNA or any continuous DNA sequence found on the chromosome," and thus "can be used to express a protein in a cell that does not normally produce it." *AMP*, 689 F.3d at 1340 (Moore, J., concurring in part). Judge Bryson similarly noted that "cDNA has a utility not present in the naturally occurring BRCA DNA and mRNA because cDNA can be attached to a promoter and

inserted into a non-human cell to drive protein expression." *Id.* at 1356 (Bryson, J., concurring in part and dissenting in part).

That reasoning applies with added force here. Unlike genomic DNA, primer pairs are designed to be used in several different laboratory-designed processes, and thus have a utility that naturally occurring DNA does not. For example, they can be used to "prime" the process of synthesizing a DNA molecule sharing a portion of the sequence of the BRCA1 or BRCA2 genes in a polymerase chain reaction, or as part of a process to determine if a patient's gene has large deletions or duplications of a part of the gene sequence, among other things. *See* Roa Decl. at ¶¶ 6-22, 30-37. As Defendants' declarant admits, even cDNA—which is patent eligible—cannot be used as a primer. Pribnow Decl. at ¶ 84.

Indeed, two of the Federal Circuit judges in the *AMP* opinion emphasized that cDNA has a distinctive utility that supports its patentability even though that utility—making a BRCA1 protein—was the same function performed by the natural DNA just in a different environment. Judges Moore and Bryson emphasized in their separate opinions that a promoter can be attached to a cDNA molecule and the resulting construct inserted into a non-human cell to produce BRCA1 protein. *AMP*, 689 F.3d at 1340, 1356. Even though the cDNA performs the same function in the new non-human cell that the native gene performs in the original human cell—*i.e.*, making BRCA1 protein—the judges found that use distinctive and one reason why cDNA was patent eligible. The human-designed pair of primers at issue in this case, in contrast, perform an entirely new laboratory function—they prime the targeted synthesis of a DNA molecule with a specific, human-defined sequence in a chemical reaction (PCR) that could never occur in the human body. Accordingly, to be consistent with the reasoning of the Supreme Court

and the Federal Circuit, the ’282 patent claims 16-17 and ’492 patent claims 29-30 relating to pairs of DNA primers must be held patentable.

3. Defendants’ Arguments Ascribe Far Too Sweeping a Scope to *AMP*.

a. Defendants’ Assertion that Patent Claims Relating to Primers Are Unpatentable Because of their Nucleotide Sequence Misreads *AMP*.

Defendants’ argument that claims 16-17 of the ’282 patent and claims 29-30 of the ’492 patent are not patentable simply because each primer in the claimed pair of primers shares a common nucleotide sequence with a segment of naturally occurring DNA (Defs’ Opp. at 1-2, 25-32, 34-37) is premised upon an overly broad interpretation of the Supreme Court’s ruling.

Engaging in characterization rather than citation, Defendants contend that the *AMP* opinion “laid down a principle that … [l]ab-generated DNA segments with the identical sequence as a native DNA segment are not patentable because they are products of nature,” and thus “held that the information (sequence) in DNA was the key.” Defs’ Opp. at 1, 35. As detailed above, the Court expressed no such holding and in fact adopted a contrary analytical construct, especially in holding cDNA patentable. Defendants further assert that the *AMP* decision held that “[t]he sequence of the DNA, and not how it is made, governs whether the DNA is an unpatentable product of nature under 35 U.S.C. § 101,” and that, “[i]f the DNA primer nucleotide sequence created in the lab corresponds to a natural DNA sequence, then it is an unpatentable product of nature under *Myriad*.” *Id.* at 1, 26. Defendants cite nothing from the Court’s decision as support for such broad statements, because there is none.

As much as Defendants would like the *AMP* holding to have the broad and sweeping effect they ascribe to it, the Supreme Court expressly refrained from making such far-reaching holdings. As discussed above, the Court’s decision is definitive. It is not based upon any similarity in genetic sequence, but upon a distinction between “a naturally occurring DNA

segment" that has been "isolated from the rest of the human genome" "by severing the covalent bonds that connect the DNA to" that genome, and DNA "created synthetically" "in the laboratory" through any of a number of "processes." *AMP*, 133 S.Ct. at 2111-12.

Moreover, Defendants' argument that the Court held that a patent claim for synthetic DNA that has the same nucleotide sequence as naturally occurring DNA is ***necessarily not*** patentable is directly at odds with the Court's statements made in relation to its separate holding that cDNA is patentable. The Court expressly rejected AMP's analogous argument that "cDNA is not patent eligible because '[t]he nucleotide sequence of cDNA is dictated by nature, not by the lab technician.'" 133 S.Ct. at 2119. It stated, "***[t]hat may be so***, but the lab technician unquestionably creates something new when cDNA is made. cDNA retains the naturally occurring exons of DNA, but it is distinct from the DNA from which it is derived," and thus is patentable. *Id*. (emphasis added). Accordingly, contrary to Defendants' argument that "the information (sequence) in DNA was the key" (Defs' Opp. at 35), neither the significant similarity between a cDNA's sequence and the sequence of its corresponding gene, nor the fact the cDNA conveys the same "information" (*i.e.*, the information needed to produce a protein) was sufficient to render cDNA unpatentable. Despite all these similarities, including "the information (sequence) in DNA," cDNA was held patentable because it was synthetically created.[17]

[17] Defendants' related argument that, because '492 patent claims 29 and 30 refer to the claimed primers as being "isolated," they must be "expressly swe[pt] in[to] the Supreme Court's [AMP] decision of 'isolated DNA'" (Defs' Opp. at 34-35), should likewise be rejected. Rather than merely refer to an "isolated DNA," like the claims held unpatentable in that case, the claims here expressly recite synthetic DNA, namely, "[a] pair of single-stranded primers." Moreover, as detailed above (Section I(B)(1), *supra*), the Court used the word "isolate" only in reference to naturally occurring DNA extracted from a human cell, and not to synthetic DNA. Also, the claims refer to the sequence of the primers as "isolated from human chromosome 13" not as "isolated DNA."

b. Defendants' Argument that the Primer Pair Claims Are Not Patentable Because They Are "Short" Segments of DNA "Indistinguishable" from Genomic DNA is Likewise Based on a Misreading of *AMP*.

Defendants' only other argument is that the primer claims are not patentable because they are short strands of DNA allegedly indistinguishable in terms of their nucleotide sequence from naturally occurring DNA removed from a human cell. Defs' Opp. at 32-33, 36. Defendants rely on a piece of dicta in *AMP* that did not even address the type of DNA at issue here. Specifically, Defendants (and their amici) rely on the highlighted language from the following portion of the Court's holding: "cDNA is not a 'product of nature' and is patent eligible under 35 U.S.C. § 101, ***except insofar as very short series of DNA may have no intervening introns to remove when creating cDNA. In that situation, a short strand of cDNA may be indistinguishable from natural DNA.***" 133 S.Ct. at 2119 (emphasis added).

As is readily apparent, however, the statement is *dictum*. The Court did not decide the issue; it merely observed that such cDNA "may" not be patentable. The Court framed its statement that way because that issue was not before the Court. Thus, at most, the Court merely noted that it was an open question whether some, unidentified short strand of cDNA "may be indistinguishable from natural DNA" and may not be patent eligible. Moreover, the statement was expressly directed at a certain type of cDNA—cDNA transcribed from mRNA from a gene containing only one exon and no introns—not before the Court.

Indeed, given the context of the Court's discussion relating to cDNA and the inherent nature of its creation, the Court's comment could only be addressing cDNA created from human

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Nor did the Court hold that "primers" "were not patentable" based on Defendants' improperly applied definition of "isolated," as Defendants assert. *Id.* at 30. No primer claims were before the Court; accordingly, the Court's opinion understandable never even uses the word "primer." *See AMP*, 133 S.Ct. at 2110-20.

genes that are so short that they have only one exon, and thus "have no intervening introns to remove ***when creating cDNA***." *Id.* at 2119 (emphasis added). Such is not the case for the BRCA1 or BRCA2 genes because, as the Court recognized, those genes have a number of exons and intervening introns. *See id.* at 2112-13, 2119. Accordingly, the Court's observation is not applicable to BRCA1 or BRCA2 cDNA, or any other synthetic DNA relating to those genes.

Defendants' related argument that the claimed "pair of single-stranded primers" are not patentable because such primers are "indistinguishable" from "natural DNA" (Defs' Opp. at 32-33, 36) is also incorrect. As set forth in detail above (*see* discussion, *supra* at Section I(B)(1(b)) a "***pair*** of single-stranded primers," especially a pair capable of synthesizing a DNA molecule having a specific sequence, do not exist in nature, but instead are created in a laboratory. They are also markedly "distinct" from naturally occurring genomic DNA for the reasons discussed above. Therefore, the claimed pair of primers are patentable.

Defendants' argument that the claimed pair of primers are "not sufficiently different" from naturally occurring DNA (Defs' Opp. at 35-37; *see id.* at 18-20) also does not withstand scrutiny. Defendants assert that there is no distinction between the two simply because they share the same nucleotide sequence as a segment of genomic DNA and follow "Watson-Crick base pairing" rules. *Id.* However, like DNA primers, cDNA are synthetic DNA molecules that likewise share the same nucleotide sequence as a segment of genomic DNA and follow "Watson-Crick base pairing" rules. Accordingly, applying Defendants' reasoning, cDNA would be unpatentable, but the Supreme Court in *AMP* upheld the patentability of cDNA and the cDNA-based patent claims. Accordingly, there is no justification for Defendants' artificial segregation of cDNA from the other forms of synthetic DNA at issue here.

4. The Method Claims at Issue are Patentable Under § 101.

Next, despite the Supreme Court's express endorsement of Judge Bryson's statement that "[a]s the first party with knowledge of the [BRCA1 and BRCA2] sequences, Myriad was in an excellent position to claim applications of that knowledge", and that "[m]any of its unchallenged claims are limited to such applications" (*AMP*, 133 S.Ct. at 2120), Defendants challenge the patent eligibility of just such method claims. (Defs' Opp. at 37-50; *see also* Amici's Opp. at 12-17.) The "method" claims asserted in Myriad's Motion—'441 patent claims 7 and 8, '857 patent claim 4, '721 patent claim 5, and '155 patent claims 2 and 4—are patent eligible under § 101 because they are not directed to a natural law or abstract mental process, but instead employ specific laboratory testing processes that apply Myriad's discovery of the BRCA1 and BRCA2 genes to develop physical steps that were not well-understood, routine, or conventional at the time the patents were filed. The claims are patentable for the additional reason that they are applications for using the novel pair of primers that are themselves patent eligible for the reasons discussed above. Myriad is thus likely to succeed in defeating Defendants' argument that these claims are not patentable.

a. The Method Claims Are Patent Eligible Because They Include More Than Mere Abstract Mental Steps and/or Routine or Conventional Steps.

Myriad's method claims are directed to *specific applications* of knowledge about the BRCA1 and BRCA2 genes. They include more than merely abstract mental steps and routine or conventional steps, and are instead directed to specific laboratory processes that utilize knowledge of the BRCA1 and BRCA2 genes to develop previously unknown techniques. Application of the Court's *Mayo* analysis demonstrates the patentability of the method claims at issue.

Mayo involved method claims that had only two steps: (1) "administering" known drugs; and (2) "determining" the resulting level of a known metabolite (6-thioguanine) in the patient. 132 S.Ct. at 1296. After these steps, the claims merely recited a "natural law," stating that "wherein" a certain "low level" of the metabolite in the blood "indicate[d] a need to increase" the amount of the drug, and a certain high level "indicate[d] a need to decrease" the amount of the drug. *Id.* at 1295, 1297-98. The Court stated that the claims accordingly did nothing more than instruct "a pre-existing audience" (physicians) to "administer" thioguanine drugs (which were already being administered before the patent filing); "determine" the level of the known metabolites in the blood, "through whatever process the doctor or laboratory wishes to use"; and finally instruct the doctor about "relevant natural laws, at most adding a suggestion that he should take those laws into account when treating his patient." *Id*. at 1297-98.

Mayo held that such claims were not patent eligible because "simply appending conventional steps, specified at a high level of generality, to laws of nature, natural phenomenon, and abstract ideas cannot make those laws, phenomenon, and ideas patentable." 132 S.Ct. at 1300. The Court held that the "administering" and "determining" steps were "well-understood, routine, conventional activity, previously engaged in by those in the field." *Id.* at 1299, 1297-98. The Court stated that the "wherein" clause contained only an abstract "suggestion that [the doctor] should take the [relevant natural] laws into account when treating his patient," and thus merely "tell[s] the relevant audience about the laws while trusting them to use those laws appropriately where they are relevant to their decisionmaking." *Id.* at 1298.

Myriad's method claims are markedly different from those in *Mayo*. The only physical steps in the *Mayo* claims involved general, conventional techniques for well-known drugs. Indeed, using thioguanine as a drug metabolite and as a biomarker (*i.e.*, a molecule that could be

analyzed in patient samples to derive clinical information) was well-known, its association with a clinical characteristic was well-known, and applications of general assay techniques to assay for this specific biomarker were well-known. In fact, even certain therapeutic ranges were well-known. The patentee's *only* contribution to the art was a refined therapeutic range.

The method claims at issue here could not be more different. Myriad discovered a brand new biomarker (the BRCA1 and BRCA2 genes) in a new indication (hereditary breast and ovarian cancer). Myriad was also the first to apply its discovery to design specific applications of generalized techniques such as PCR and DNA sequencing to develop new assays for this new biomarker.

Defendants' argument rests on a flawed reading of *Mayo* and an incorrect application of that case here. In *Mayo*, the patentee's "invention" involved no new physical assay or even a modification to an existing assay. As the Court stated, the physical assay elements of the claims involved were "well-understood, routine, conventional activity ***previously engaged in*** by scientists who work in the field" or "by those in the field. 132 S.Ct. at 1298, 1299 (emphasis added). *Mayo* was not a case where general assay principles were well-known, but the application of those principles to a new biomarker was unknown. To the contrary, the biomarker and various specific techniques for assaying the particular biomarker were "previously engaged in," and all details of the physical assay were well-known at the time of the filing of the patents. *Id.*

This case presents opposite facts and compels the opposite conclusion. Defendants spend several pages arguing that Myriad's claims recite only the general assay steps of amplifying, sequencing, probing (by hybridization), and screening (Defs' Opp. at 43-48), but that is simply not the case. To the contrary, the claims are limited to ***specific application*** of these techniques to

the ***new biomarkers*** Myriad discovered. Before Myriad's discovery, amplifying, sequencing, probing (by hybridization), and screening the BRCA genes was in no way a well-understood, routine, or conventional activity. Indeed, because the genes' sequence was unknown, it was a near statistical impossibility that anyone could design a process to amplify segments of that unknown sequence. Myriad's discovery of the BRCA1 and BRCA2 sequences was necessary to allow the creation of new primers, probes, and amplicons specifically designed for analysis of the new biomarkers. This in turn allowed for new applications of determining a patient's cancer risk using these reagents and techniques. Those specific new applications—new primers, probes, and amplicons, and the sequencing of such amplicons—are expressly recited as limitations in the asserted method claims.

Defendants challenge the patentability of claim 7 of the '441 patent, arguing that "Claim 7 requires simply applying the steps that there be hybridization and 'detection' of a difference between the wild type DNA sequence and an allele (mutation). A broad 'detecting' step is insufficient under *Mayo*, and appending the well-known hybridization of a probe is a routine step." Defs' Opp. at 47. However, instead of generically reciting the steps of "hybridization" and "detection," the claim actually recites "hybridizing a *BRCA1 gene probe* which *specifically hybridizes* to a *BRCA1 allele*," and "detecting the presence of a hybridization product" (*i.e.*, the product of the specific hybridization of the BRCA1 probe and a target DNA molecule). Similarly, claim 8 of the '441 patent does not generically recite the step of "amplification," the general principles of which were routine. Rather, Claim 8 recites "amplifying all or part of ***a BRCA1 gene*** from said sample."

The steps in every claim thus require application of the previously unknown BRCA1 or BRCA2 gene sequences to design primers or probes based on those specific sequences so that

they will work to amplify and/or hybridize to parts of those genes, and nearly all the claims further require sequencing of the amplified products (and in some cases specifically require "Sanger" sequencing) for a comparison to a normal sequence. *See* '441 patent, claims 7 & 8; '721 patent, claim 5; '155 patent, claims 2 & 4; '857 patent, claim 4. Some claims further require a comparison to determine if certain specific nucleotides have certain specific differences. *See* '721 patent, claim 5; '155 patent, claims 2 & 4. In short, the claims recite specific chemical assays that were not ***routine*** at the time the patents were filed because it was ***impossible*** as a practical matter to create or perform the assays without knowing the BRCA1 and BRCA2 sequences.

Thus, rather than being similar to the claims at issue in *Mayo*, the method claims here are analogous to those held patentable by the Supreme Court in *Diamond v. Diehr*, 450 U.S. 175 (1981). In that case, the patentee claimed a new process for curing rubber based on a mathematical equation called the "Arrhenius equation." The general principles of curing rubber were well-known at the time of the patentee's filing. But application of the Arrhenius equation to those processes altered them, resulting in a new and improved process. It was still a process for curing rubber, but a new rubber curing process integrating the equation. *See id.* at 187-93.

For diagnostic method claims under *Mayo*, the ultimate question can thus be boiled down to whether *all* physical assay elements *as claimed* were well-known and routinely practiced in the field *at the time of the patentee's filing*. In *Mayo*, if one set aside the statement of scientific fact contained within the claims (*i.e.*, a high level of thioguanine indicates the dose should be reduced and a low level indicates the dose should be increased), one was left with a laboratory process that in every detail was routinely practiced in the art at the time Prometheus filed its application.

In contrast, in this case, the methods as specifically claimed were not routine, but were actually impossible as a practical matter before Myriad's discovery of the BRCA1 and BRCA2 sequences.[18] The Supreme Court in *AMP* noted that such method claims or other "new applications" of the knowledge of the BRCA1 and BRCA2 sequences are patentable, quoting the statement from Judge Bryson of the Federal Circuit that, "[a]s the first party with knowledge of the [BRCA1 and BRCA2] sequences, Myriad was in an excellent position to claim applications of that knowledge" regarding those sequences. *Id.* at 2120.[19]

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[18] Defendants attempt to convert the ruling in *Mayo* into a question of whether claim elements ***beyond*** the recited natural law would have been "obvious" in view of that law under § 103's obviousness inquiry (*see* Defs' Opp. at 40). Such an approach contravenes *Mayo*'s express holding. *Mayo* focused the § 101 patentability analysis in this regard on whether the "routine, conventional activity" in the claims had been "***previously engaged in*** by scientists," and thus focused on whether the precise activities as claimed were already routine and conventional ***before the patent*** was filed. 132 S.Ct. at 1298 (emphasis added). The claims recited laboratory processes that were routine and conventional in every detail; the only thing added was the law of nature. *See id.* at 1297-98. Given that context, the proper inquiry is whether the steps as specifically recited beyond the natural law were ***already*** well-understood, routine and conventional ***at the time of the filing*** of the patent, not whether those steps ***would have been*** obvious after learning of the natural law. For example, while amplification and sequencing were generally known, the details of how to apply these techniques to BRCA1 and BRCA2 testing were not "well-known, routine and conventional" (they were in fact completely unknown). Defendants essentially admit as much by arguing that applying them to BRCA1 would have been obvious, ***but only in view of Myriad's discovery*** of the gene sequences. *See* Defs' Opp. at 44-45.

[19] Defendants also fault the claims for *including* at least one "abstract mental process" or "mental process" of "comparing" two DNA sequences (Defs' Opp. at 38, 40-41, 43, 44), but that fact is of no moment. In that regard, the Federal Circuit in the *AMP* lawsuit held, based on *Mayo* and other precedent, that if the steps in the claimed methods included steps ***only*** for "comparing or analyzing nucleotide sequences," then they "***are only directed to*** the mental abstract process of comparing two nucleotide sequences," and thus are "patent-ineligible processes." *AMP*, 689 F.3d at 1334-35 (emphasis added). Thus, the fact that the claims include one or more such abstract mental steps is not dispositive unless *all* steps claimed "are only directed to" an "abstract mental process." Because the claims here include concrete, physical steps, they cannot be held patent ineligible on this basis. Defendants also incorrectly suggest that '857 patent claim 4 is not patent eligible because, as a claim stated in "Markush" format, it recites a few purely "mental processes" as possible ways to detect genetic alterations. They refer to the recitations of "screening" for certain alterations in this regard. Defs' Opp. at 46 & n.10. Defendants, however, ignore that claim 4 mandates that each of the possible steps listed, including each "screening" step, must be "an assay." This requirement means that there must be a physical test and a mental

b. In Any Event, the Asserted Method Claims Are Patent Eligible Because they Recite Steps for Using Patentable Synthetic DNA Primers or Probes.

Even assuming for the sake of argument that the method claims contained only routine and well-known steps (which they clearly do not), they would nevertheless be patent eligible for the simple reason that they include the use of patentable synthetic DNA. In particular, those claims recite applications for using novel synthetic DNA primer pairs, amplicons, and/or probes based on the BRCA1 or BRCA2 genes that include one or more physical steps, such as amplification, hybridizing, and/or sequencing.[20] As the Federal Circuit held in *AMP*, "once one has determined that a claimed composition of matter is patent-eligible subject matter, applying various known types of procedures to it is ***not merely applying conventional steps to a law of nature***," and thus such a method claim is "patent eligible" under § 101. *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 689 F.3d 1303, 1336 (Fed. Cir. 2012) (emphasis added). Importantly, the Federal Circuit made that holding after the case had been remanded by the Supreme Court (*see id.* at 1308, 1333-35) for reconsideration in light of the Supreme Court's decision in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S.Ct 1289 (2012), and that analysis was not affected by the Supreme Court's *AMP* ruling.

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process will not suffice. The patent refers to a number of such "screening assays." *See, e.g.*, '857 patent at col. 28, line 16 to col. 29, line 40.

[20] '441 patent, claim 8 (requiring use of "a set of primers to produce amplified nucleic acid"—*i.e.*, amplicons—from "all or part of BRCA1 gene" and "sequencing the amplified nucleic acids"); '721 patent, claim 5 ("the BRCA1 gene or fragment thereof is amplified prior to sequencing"); '155 patent, claims 2 & 4 ("amplifying a DNA fragment of an individual's BRCA1 coding sequence using an oligonucleotide primer which specifically hybridizes to sequences within the gene" and "sequencing said amplified fragment"); '441 patent, claim 7 ("hybridizing a BRCA1 probe which specifically hybridizes to a BRCA1 allele"); '857 patent, claim 4 (requires use of an "assay" that includes "amplifying all or part of the BRCA2 gene ... to produce an amplified sequence and sequencing the amplified sequence" or "hybridizing a BRCA1 gene probe to genomic DNA"). An amplicon is variously referenced in these claims as an "amplified nucleic acid," "amplified fragment," or "amplified sequence." Also, as set forth in Myriad's Motion, "probes" are similar to primers. Roa Decl. at ¶ 31.

In challenging the patentability of the method claims, Defendants rely on the same legally incorrect arguments, refuted above, that the pair of primer claims are not patent eligible. Specifically, Defendants assert that the method claims are not patentable based on the Supreme Court's *AMP* decision because the "primers," "amplicons," and "probes" "encompass unpatentable subject matter of 'isolated DNA'" or "unpatentable products of nature." Defs' Opp. at 37-38, 41-43, 45-47; *see also* Amici's Opp. at 14-16. Defendants' arguments of non-patentability under § 101 are incorrect and should be rejected for the reasons discussed in section I(B), *supra*.

Notably, Defendants effectively concede that, if the synthetic primers, amplicons, and probes are patentable, then all of the method claims at issue are patentable. *See* Defs' Opp. at 42 (concurring that a method claim is patent eligible under the Federal Circuit's *AMP* decision if it requires the use of a "non-naturally occurring composition"). Defendants also do not deny that the Federal Circuit made that holding while expressly considering and applying the Supreme Court's decision in *Mayo*, and thus nothing in *Mayo* alters that conclusion. *See* Defs' Opp. at 42-43. Indeed, they recognize that *Mayo* applies to render a claim non-patent eligible only if the claim merely recites a "law of nature," "phenomenon of nature," or an "abstract mental process." *Id.* at 38-41. Because the claims here all utilize synthetic DNA primers, amplicons, and/or probes—which, as demonstrated above, are not merely laws or phenomena or even products of nature—*Mayo* is simply inapplicable here.[21]

[21] The post-*Mayo* decisions cited by Defendants (*see* Defs' Opp. at 49-50; *see also* Amici's Opp. at 15) do not alter these conclusions. Defendants primarily refer to *Aria Diagnostics*. In *Aria*, the district court denied a motion for preliminary injunction based in part upon the determination that there was a "substantial question" regarding the patent eligibility of the asserted claims. 2013 WL 4033479 at *6. However, the district court's decision in that regard was vacated and remanded by the Federal Circuit for further consideration in light of the Supreme Court's *AMP* decision. *Aria Diagnostics, Inc. v. Sequenom, Inc.*, No. 2012-1531, 2013 WL 4034379 at *6

c. Defendants' Arguments Relating to Claims Not at Issue and Concerning Preemption are Inapposite.

Defendants' references to the fact that some of the patent claims at issue—'441 patent claims 7 and 8 and '857 patent claim 4—"depend from" the '441 patent claim 1 and '857 patent claims 1 and 2 held not patentable by the district court and Federal Circuit in the *AMP* lawsuit (Defs' Opp. at 38, 45, 47, 48), is simply irrelevant. It is a basic principle of patent law that "dependent" claims are narrower than the independent claim from which they depend, and thus their patentability must be separately assessed. *See Wahpeton Canvas Co. v. Frontier, Inc.*, 870 F.2d 1546, 1552 n.10 (Fed. Cir. 1989) ("a necessarily narrower dependent claim may be valid when the claim from which it depends is not"). Specifically, '441 patent claim 8 incorporates claim 1, but is much narrower because it requires the use of a "set of primers" to "produce amplified nucleic acids" and "sequencing the amplified nucleic acids." '441 patent claim 7 is similar except that it requires "hybridizing a gene probe" rather than primers. '857 patent claim 4 incorporates claim 2, but is narrower because it requires using an "assay" that includes either "amplifying" and "sequencing" or "hybridizing a BRCA1 gene probe." As demonstrated above, these BRCA-specific, non-routine physical assay steps confer patentability on these dependent

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(Fed. Cir. Aug. 9, 2013). Since the Federal Circuit was reviewing the denial of a preliminary injunction, there would be no reason for the court to vacate and remand if it thought that the Supreme Court's *AMP* decision made the claims at issue even more subject to challenge. Defendants' reference (Defs' Opp. at 49-50) to *Tessenderlo Kerley, Inc. v. Or-Cal, Inc.*, 2012 U.S. Dist. LEXIS 78044 (N.D. Cal. June 5, 2012), is even more misplaced. The court merely denied a motion for summary judgment on patentability because "more discovery [was] needed" to determine if the claimed steps were merely "routine and conventional" steps for applying a natural law. *Id.* at *16. There was no substantive ruling on patentability, and the court did not deny a motion for a preliminary injunction based on that issue.

claims by distinguishing them from the broader independent claims the Federal Circuit invalidated because they contained ***only*** abstract mental steps.[22]

Next, Defendants make a few passing comments that the method claims "effectively preempt the ability to read and compare the natural BRCA DNA" and thus "preempt[s] the use of the natural law," and somehow "exclude scientists from reading patients' genetic information" because "sequencing equipment simply cannot exclude reading a single nucleotide base in a gene sequence." Defs' Opp. at 38, 43, 48. The claims do not have the broad, preclusive effect that Defendants ascribe. To the contrary, the claims are limited to applications of Myriad's knowledge gained through their discovery of the BRCA1 and BRCA2 genes. The method claims require, for example, the specific synthesis (through amplification) of DNA having at least a portion of the sequence of the BRCA1 or BRCA2 gene, or the use of a synthetic probe molecule specific for BRCA1- or BRCA2-specific DNA.

The claims thus do not preempt ***any use*** of naturally occurring DNA extracted from a human cell, including sequencing. Further, there are technologies available that utilize unenriched, natural DNA extracted from a patient's cells and do not require production of

[22] Defendants' reliance on the district court's ruling in the *AMP* case on '441 patent claim 1 (Defs' Opp. at 48) is misplaced. Claim 1 is not at issue here and thus the ruling is inapplicable. In any event, that court's reasoning was rejected by the Federal Circuit. Defendants state that the district court held that claim 1 would not be patentable even if it "were read to include the transformations associated with isolating and sequencing human DNA." *Id.* The Federal Circuit rejected that approach. The Federal Circuit held that the claim was not patentable because the only step in the claimed method was "comparing" one BRCA1 sequence with another BRCA1 sequence, which was unpatentable because it "recites nothing more than the abstract mental steps necessary to compare two nucleotide sequences." *AMP*, 689 F.3d at 1334-45. Contrary to the district court's holding on which Defendants' rely, the Federal Circuit held that "the application of a formula or abstract idea in a process may describe patent eligible subject matter, [but] Myriad's claims [at issue in that case] do not apply the step of comparing two nucleotide sequences in a process" because the claims include no physical steps, like "sequencing the BRCA DNA molecule." *Id.*

synthetic DNA for subsequent analysis that are not implicated by Myriad's patents.[23] The claims also do not prevent sequencing of genetic information generally because the claims require the amplification of all or part of the BRCA1 and BRCA2 genes, and thus there is no preclusion on the amplification and/or sequencing of any other genes.[24]

C. Myriad is Likely to Succeed in Proving Infringement.

1. Defendants' Noninfringement Arguments of '282 Patent Claim 16 and '492 Patent Claim 29 are Based on an Erroneous Claim Construction.

Defendants' noninfringement arguments hinge on a facially erroneous construction of '282 patent claim 16 and '492 patent claim 29. Defendants acknowledge that the plain claim language requires that the nucleotide sequence of the claimed primers merely be "derived from" the DNA sequence in "chromosome 17q" (for claim 16) or "isolated from" the DNA sequence in "chromosome 13" (for claim 29). Defendants do not dispute that their primers are used to amplify the BRCA1 and BRCA2 genes, and that each include nucleotide sequence is derived or isolated from chromosome 17q and 13 (where those genes are located). Defs' Opp. at 79-80, 81-82. Indeed, their declarations expressly admit that fact. *See* Elliott Decl. at ¶¶ 15-18 (Ambry's primers "contain some sequence that hybridizes to the BRCA gene sequence"); Mittelman Decl. at ¶ 16 (GBG's primers include "sequences that hybridize to the BRCA gene").[25]

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[23] Those technologies include gene expression profiles, untargeted single-molecule sequencing, and protein truncation testing. *See, e.g.*, https://www.nanoporetech.com/technology/analytes-and-applications-dna-rna-proteins/dna-sequencing-applications; https://www.nanoporetech.com/technology/analytes-and-applications-dna-rna-proteins/dna-an-introduction-to-nanopore-sequencing (both last visited Aug. 30, 2013).

[24] Further, as detailed in the Amicus Brief of the Philadelphia Intellectual Property Association before the Supreme Court (Mangum Decl., Ex. F at 17-27), there is a generally recognized exception to application of patents to academic research. Moreover, Myriad has consistently declined to enforce its patents against those engaged in legitimate academic endeavors. *See infra* at II(C)(2)(c).

[25] Instead, Ambry asserts only that other primers not at issue here—its "sequencing primers" used in a separate and subsequent sequencing operation—"contain no sequence whatsoever

Defendants instead assert that, as an additional feature commonly used and familiar to those of skill in the art for many years, their BRCA1 and BRCA2 primers also include "adaptor," "bar code," and/or "tag" sequences appended to the end of the primers that will not hybridize to a segment of the BRCA1 and BRCA2 genes. Defs' Opp. at 79-80, 81-82. Defendants argue that, because the entire sequence of each primer is not "derived ***wholly*** from" the nucleotide sequences in chromosome 17q or chromosome 13, their primers do not infringe these claims ***if*** the claim language "derived from" and "isolated from" is interpreted to mean "derived wholly from." *Id.* The conditional "if" clause dooms Defendants' argument.

The plain claim language, and the description in the '282 patent and '492 patent specifications, unequivocally demonstrate the impropriety of Defendants' claim construction. The plain meaning of "derive" is "to receive or obtain from a source or origin," and "isolate" means "to set or place apart; detach or separate so as to be alone." Dictionary.com. None of these plain meanings limit the claim language in the manner Defendants propose. These meanings indicate only that the primers will have material obtained or received from a source ("derived" from chromosome 17q) or that the primers are "separate" or "apart" from the whole chromosome (chromosome 13). Neither meaning precludes the use of appended molecules or nucleotides to the primer ends.

Other parts of the claim language provide further insight on this limitation. They require that "the use of said primers in a polymerase chain reaction results in the synthesis of DNA having all or part of the sequence" or "all or at least 15 contiguous nucleotides" "of the BRCA1 gene" or "BRCA2 gene." In other words, the primers need only have enough of a BRCA1- or

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derived from chromosome 17q." Defs' Opp. at 79. However, Myriad did not assert that such non-specific sequencing primers infringed claim 16; only that its preparation of DNA samples by amplification infringed that claim (Plfs' Mot. at 16-20), and Ambry admits that those primers contain nucleotide sequences from that chromosome.

BRCA2-specific nucleotide sequence to allow for synthesis of part of the BRCA1 or BRCA2 sequence. Consequently, other nucleotides attached to the end of such a primer do not change the fact that a pair of such primers will synthesize a nucleic acid having a portion of the BRCA1 or BRCA2 sequence.

The patent specifications even more explicitly state that other elements may be added to primers to allow for downstream analysis of the PCR product. They state that additional nucleotide sequences beyond the BRCA1 and BRCA2 gene sequences are contemplated as part of the claimed primers or any other claimed polynucleotide. They both refer to "primer pairs of the present invention" as being composed of synthetically made lengths of multiple nucleotides (*i.e.*, polynucleotides). '282 patent at col. 16, lines 23-28, 42-48; '492 patent at col. 15, lines 10-15, 29-36. Both patents also specifically provide that "***[t]he polynucleotide compositions of this invention*** include … synthetic forms …, and ***may be chemically or biochemically modified or may contain non-natural or derivatized nucleotide bases***, as will be readily appreciated by those skilled in the art. ***Such modifications include, for example, labels***, [and other modifications]." '282 patent at col. 19, lines 51-57 (emphasis added); '492 patent at col. 18, lines 36-42 (emphasis added). The patents thus expressly state that the claimed primers may be "modified" to have additional nucleotide sequences, including "non-natural" nucleotides such as "labels." Accordingly, the patents mandate that labels—like the "bar codes" and "tags" Defendants add to their primers—and other "non-natural" nucleotides, like the "adaptors" Defendants use to attach those bar codes and tags, are part of the claimed primers. Defendants simply ignore this language from the patents when making their contrary claim construction argument.

The patents also disclose laboratory systems directly analogous to such "adaptors." They describe the use of "adapter" DNA sequences ligated onto other DNA and the use of such

adapter sequences to prime a PCR amplification reaction. '282 patent, col. 11, lines 36-58; '492 patent at col. 10, lines 22-43. These adapters are described as having tags attached in the form of biotin that allow for later analysis (specific capture with avidin) of the nucleic acids generated by use of the primers. *Id.* The patents similarly describe an example where "universal primer sites" are added along with a protein (alkaline phosphatase) that can later be detected or captured. '282 patent, col. 61, lines 40-56; '492 patent col. 48, lines 17-34.

Accordingly, adding nucleotides to a BRCA1 or BRCA2-specific primer to facilitate later sequencing does not change the fact that the primer's sequence is "derived" from chromosome 17q or "isolated from" chromosome 13 any more than would attaching biotin to a BRCA1-specific primer to facilitate later capture of the PCR product for further analysis. Moreover, adding elements to an item covered by a patent has never been a valid defense to infringement. *Amstar Corp. v. Envirotech Corp.*, 730 F.2d 1476, 1482 (Fed. Cir 1984) ("Modification by mere addition of elements of functions ... cannot negate infringement without disregard to the long-established, hornbook law.").

The patents contain other language that similarly demonstrates that the claimed primers are not limited to chromosomal sequences. The patents state that, "to facilitate subsequent cloning of amplified sequences, primers may have restriction enzyme site sequences appended to their 5′ ends." '282 patent at col. 16, lines 36-38; '492 patent at col. 15, lines 23-25. Defendants seek to avoid the impact of this language by arguing that it refers specifically only to the primers used in cloning, and that cloning is not specifically referenced in claims 16 or 29. Defs' Opp. at 78, 81. Regardless of the particular application discussed, this statement in the patents, along with the other statements in the specification described above, demonstrates that the claimed

primers are generally contemplated to include appended molecules, including nucleotide sequences other than those from chromosomes 17q and 13.

The patents contain even more language further confirming that fact. They discuss other types of synthetic polynucleotides called "probes" that are similar to primers. In regard to such probes, the patents state that the claimed "probes will include an isolated polynucleotide attached to a label or reporter molecule," and that "[s]uitable labels, and methods for labeling probes and ligands are well known in the art, and include, for example, radioactive labels … fluorescent groups, [and] chemiluminescent groups," among others. '282 patent at col. 21, lines 63-67; col. 29, lines 21-27; '492 patent at col. 20, lines 46-50; col. 27, line 63 to col. 28, line 6.

Accordingly, the patents preclude the claim construction that Defendants rely upon for their only argument of noninfringement of '282 patent claim 16 and '492 patent claim 29. Defendants' noninfringement argument, which requires the addition of a limitation not contained in the plain claim language or supported by the patent specifications—namely addition of the adverb "wholly"—lacks merit and Myriad is likely to succeed in proving infringement.

2. Defendants Fail to Address Myriad's Infringement Claims Relating to '282 Patent Claim 17 and '492 Patent Claim 30.

Defendants offer no response to Myriad's infringement claims regarding '282 patent claim 17 and '492 patent claim 30, other than the same fatally flawed claim construction addressed above. As Defendants acknowledge, these claims incorporate the language from '282 patent claim 16 and '492 patent claim 29, respectively. Because claims 17 and 30 thus include all of the requirements of claims 16 and 29, Defendants first reiterate the same erroneous argument that they cannot infringe because their primers and amplicons "are not ***wholly*** derived" or "isolated ***wholly*** from" the nucleotide sequence in the BRCA1 or BRCA2 genes. Defs' Opp. at 80, 82 (emphasis added).

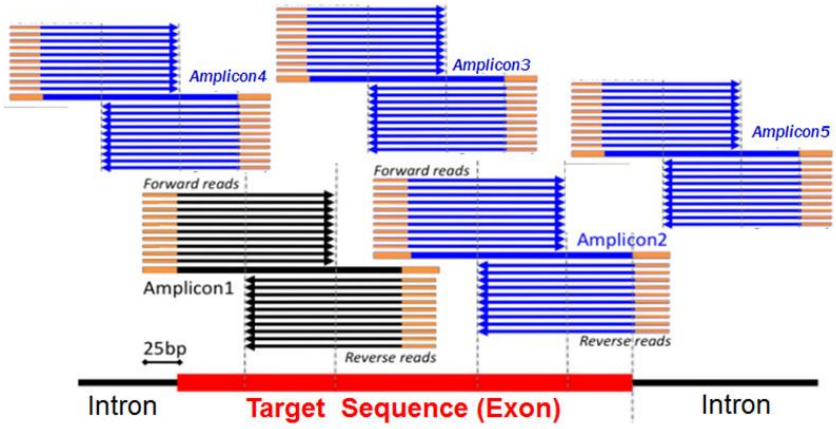
Otherwise, Defendants address only an aspect of their preparation of synthetic DNA samples that is not part of Myriad's infringement claim; they thus fail to rebut Myriad's proof of infringement. Claims 17 and 30 differ from the claims on which they depend (claims 16 and 29, respectively) because they require that the nucleotide sequence of a set of the primers, or the amplicons produced by the primers, include a sequence taken from that set forth in "SEQ ID NO:1." Defendants acknowledge that this is the sequence in the cDNA for the BRCA1 or BRCA2 genes (for the '282 patent and '492 patent, respectively) and, as a result, the claimed primers or the set of amplicons they produce do not include any part of the nucleotide sequence from the introns in that gene, and that are naturally present in genomic DNA. Defs' Opp. at 80, 81; *see* Plfs' Mot. at 19, 20.

Precisely because of this additional limit, Myriad did not argue infringement of these claims on the basis that ***every one*** of the primer pairs used by Defendants have such a sequence, or because ***every one*** of the amplicons that they produce have such a sequence. Instead, Myriad asserted infringement because "***[a]t least some*** of Ambry's [and GBG's] ***primer pairs*** have a nucleotide sequence complementary to ***only the exons*** in the BRCA1 [or BRCA2] gene," and because "such primer pairs ***will act to produce DNA molecules*** [*i.e.*, amplicons] whose relevant nucleotide sequence shares similarity to ***only part of an exon*** in the BRCA1 [or BRCA2] gene." Plfs' Mot. at 19, 20 (emphasis added). As Myriad demonstrated, some of the primer pairs used for BRCA1 and BRCA2, and the resulting amplicons produced, cannot include part of an intron sequence because "[s]ome of the exons in each gene are so long that, when the entire gene is fragmented for PCR, some of the resulting fragments consist only of exons (*i.e.*, without any intron fragments). As a result, the entire nucleotide sequence in the primer pairs for those exon fragments, and the resulting amplified DNA molecules, will inevitably share sequence similarity

only with part of an exon" and will not include the nucleotide sequence from any part of an intron. *Id.* at 18 n.7; Roa Decl. at ¶¶ 12-16.[26]

Defendants ignore these specific primers and their produced amplicons accused of infringement. Importantly, Defendants do not deny any of the Myriad's underlying factual statements. *See* Defs' Opp. at 80, 82. Defendants instead argue only that some of their primers and amplicons "contain intronic sequences" that "are, of course, not contained in cDNA." *Id.* at 80; *see id.* at 82. Further, their declarants admit that Defendants use primers to amplify the sequence of "all exons" in the BRCA1 and BRCA2 genes and, for each of those exons, "the entire exon" is "covered" or "fully covered" by the amplicons produced by the primers. Elliott Decl. at ¶ 10; Mittleman Decl. at ¶ 17. Defendants accordingly admit that they use primers and produce amplicons that cover portions of the large exons in each gene. As a necessary consequence of that activity (unrebutted by Defendants), Defendants must use at least one set of primers that has no intronic sequences, and those primers must produce amplicons that include no intronic sequences. Indeed, Ambry's declarant included an illustration showing that fact (reproduced below):

[26] This argument should not be misunderstood to suggest that claims 17 and 30 are necessarily limited to primers and amplicons that have ***only*** BRCA1- or BRCA2 exonic sequence (without any tags, labels, or adaptors). Instead, the claims merely require that the primers produce an amplicon that excludes intronic sequences. This is what differentiates and narrows the dependent claims from the independent claims, which additionally encompass primers that produce amplicons that include intronic sequences.



Elliott Decl. at ¶ 10. As shown in the illustration, the entire nucleotide sequence of "Amplicon 3," including the primer pairs shown in the lighter color on the right and left sides, falls only within the "Exon" and thus the primers and the amplicons contain no intron sequences. Myriad thus is likely to succeed on the merits on infringement of these claims as well.

3. Defendants' Assertion of Noninfringement of '441 Patent Claim 8 and '857 Patent Claim 4 Lacks Merit.

Defendants' assertion that they do not infringe '441 patent claim 8 or '857 patent claim 4 likewise lacks merit. Defendants' argument in this regard is based on an erroneous construction of the claim language that is directly contrary to the patent's definition of that language. As Defendants admit, these claims require a comparison of the "BRCA1 gene" or the BRCA2 gene sequence to a "wild-type" BRCA1 or BRCA2 nucleotide sequence. Defs' Opp. at 83, 85.

Defendants first erroneously argue that they do not infringe because they "do not utilize patient mRNA or cDNA" (*id.* at 83), presumably meaning that they do not analyze mRNA or cDNA molecules as part of their infringing activities. However, the claim language is not limited to physical analysis of either "mRNA" or "cDNA" molecules. The claims are instead drawn more broadly to any analysis that involves "amplifying all or part of a BRCA1 gene" or "BRCA2 gene" "from said sample," such as by "using a set of primers," "to produce amplified

nucleic acids" or "an amplified sequence" and sequencing the amplified nucleic acids" or "the amplified sequence."

Indeed, the patent specifications expressly define that the claim terms "BRCA1 gene" and "BRCA2 gene" "refer to polynucleotides," and that the "[t]he polynucleotide compositions of this invention include RNA, cDNA, genomic DNA, ***synthetic forms***, and mixed polymers" among others. '441 patent at col. 19, lines 30-32, 55-60 (emphasis added); '857 patent at col. 18, lines 14-16, 39-43 (emphasis added). Thus, in addition to methods involving RNA, cDNA, and genomic DNA, the claim terms by definition expressly include methods involving all "synthetic forms" of DNA of the BRCA1 and BRCA2 genes, such as those created by the use of synthetic primers that produce synthetic amplicons, both of which have nucleotide sequences from the BRCA1 and BRCA2 genes. Because Defendants' processes involves the amplification (*i.e.*, synthesis of nucleic acids having portions of the BRCA1 or BRCA2 sequences) and sequencing required by the patent claims, the fact that Defendants do not use particular examples of molecules that ***could*** be analyzed instead is irrelevant.

Indeed, it was Defendants' use of gene sequences from these synthetically created molecules that Myriad identified as infringing. Plfs' Mot. at 20-23. Defendants do not deny that they use such gene sequences to compare to the wild-type sequences. *See* Defs' Opp. at 83-84. Based on the definition of the claims terms mandated by the patent specifications, Defendants perform the methods claimed and thus infringe.

Next, Defendants turn to their sequence analysis and assert that they do not infringe because, although they compare the genetic sequence of the BRCA1 or BRCA2 genes from the patient to the genetic sequence of the wild-type of those genes as the claims require, they "compare patient sequences to the sequence of the entire human genome," and thus purportedly

do not infringe because they compare other genes in addition to the BRCA genes. Defs' Opp. at 83-85. However, as they acknowledge, the claims at issue recite methods that include a series of steps, and the claims use the transitional word "comprising" before reciting those steps. As Defendants admit, this means that the claims are "open-ended" and "inclusive," and thus encompass anything that includes additional actions or steps beyond those required in the claims. *Id.* at 84. Specifically, a claim using "the signal 'comprising' ... is generally understood to signify that the claims do not exclude the presence in the accused apparatus or method of factors in addition to those explicitly recited." *Vivid Tech., Inc. v. American Sci. & Eng., Inc.*, 200 F.3d 795, 811 (Fed. Cir. 1999). Moreover, as the Federal Circuit has repeatedly held, an accused infringer cannot avoid infringement by asserting that it performs additional steps or actions. "Modification by mere addition of elements of functions ... cannot negate infringement without disregard to the long-established, hornbook law." *Amstar*, 730 F.2d at 1482.

The sole case on which Defendants rely for their argument—*Dippin' Dots, Inc. v. Mosey*, 476 F.3d 1337 (Fed. Cir. 2007)—is inapposite. In that case, the court held that, although the six process steps in that case were prefaced by the phrase "comprising," the step at issue had to be performed exactly as stated because it required the physical formation of "beads." Based on statements made in the patent, "the patentee ha[d] narrowly defined the claim term" at issue ("beads"), and the term could not be "broadened" because the patent made clear that the process at issue must produce "beads and only beads" (and could not include the production of irregularly shaped particles). Under those unusual circumstances, the court held that the claimed step at issue excluded making beads along with irregularly shaped particles. *Id.* at 1343.

The applicable principle is explained thoroughly in *Northern Telecom Ltd. v. Samsung Electronics Co.*, 215 F.3d 1281 (Fed. Cir. 2000). The court stated that, "if a patent requires A,

and the accused device or process uses A and B, infringement will be avoided only if the patent's definition of A excludes the possibility of B. Statements simply noting a distinction between A and B are thus unhelpful: what matters is not that the patent describes A and B as different, but whether, according to the patent, A and B must be mutually exclusive." *Id.* at 1295-96 (citations omitted).

Defendants point to no language in the patents here stating that analyzing the sequence of the BRCA1 and BRCA2 genes must be done by analyzing "only" those sequences to the exclusion of all others in all instances. Defendants cite only the unremarkable statements that analyzing the BRCA genes means that the BRCA gene sequences must be analyzed for various possible variations and mutations. *See* Defs' Opp. at 83-84. Also, unlike in *Dippin' Dots,* Defendants point to nothing in the patent demonstrating that analyzing other genes in addition has any bearing on, and defeats the purpose of, analyzing the sequence of the BRCA genes. Defendants' claim constructions are erroneous and contrary to hornbook law. Myriad is likely to succeed on the merits on infringement of these claims as well.

4. Defendants' Argument of Noninfringement of '721 Patent Claim 5 and '155 Patent Claims 2 and 4 is Not Well Founded.

Defendants' argument of noninfringement of '721 patent claim 5 and '155 patent claims 2 and 4 is essentially the same as the argument just addressed, and should be rejected for the same reason. As Defendants acknowledge, these claims require comparing certain parts of a patient's BRCA1 nucleotide sequence to a normal BRCA1 sequence. Defendants refer to what parts of the gene must be included in the compared sequences as "contiguous cDNA sequences" because the comparison includes either "SEQ ID NO: 1" or "SEQ ID NO: 263," which is the sequence in only the exonic parts of BRCA1. Defs' Opp. at 85.

Defendants argue that they do not infringe "because neither [of them] compares patients' amplified sequences to a contiguous cDNA sequence of BRCA1" only. *Id.* They cite to their declarants' statements that they instead compare the patients' sequences to the entire genome; that is, they compare the exons in all of the genes, including the exons in BRCA1. *Id.* (and cited Elliott Decl. at ¶¶ 32-34 & Mittelman Decl. at ¶ 20). Accordingly, Defendants' noninfringement argument is that they do not infringe because they perform comparisons of sequences ***in addition*** to those required by the claims.

However, as with the earlier discussed claims, '721 patent claim 5 and '155 patent claims 2 and 4 are method claims including certain recited steps, prefaced by the open-ended word "comprising." As set forth above, and as Defendants admit, such claims necessarily encompass any method that makes the comparison required by the claims as well as any other comparisons. As a matter of law, Defendants cannot avoid infringement when they admittedly perform the sequential comparison of the exonic part of the BRCA1 gene as required by the claims, by merely also performing a sequential comparison of the introns in the BRCA1 gene and the exons in additional portions of the human genome. Accordingly, Myriad is likely to succeed in proving infringement of these claims.

5. Ambry's Noninfringement Argument of '441 Patent Claim 7 and '857 Patent Claim 4 is Based on an Erroneous Claim Construction.

Ambry asserts noninfringement of '441 patent claim 7 on a basis precluded by its own claim construction and by the patent itself. Citing the patent specification for support, Ambry argues that the language "a BRCA1 gene probe which specifically hybridizes to a BRCA1 allele" should be interpreted "to mean 'a BRCA1 gene probe that hybridizes ***either to the wild-type BRCA1 allele*** or a sequence of a known mutation of the BRCA1 gene sequence which predisposes to certain cancers." Defs' Opp. at 86 (emphasis added). Ambry then asserts that it

does not infringe because it "do[es] not use ... probes specific for any known variations of BRCA1 that predispose a patient to certain cancers." *Id.* at 87. However, Ambry neglects to mention that the claim encompasses the use of the first type of probe Ambry admits is covered by the claim—normal or "wild-type" probes—and that Ambry admittedly uses such probes.

Indeed, Ambry's declarant on the issue—Mr. Elliot—states that Ambry does not use "probes that detect a specific mutant" (as Ambry states in its opposition), but he admits that "Ambry uses probes specific for the wild-type BRCA genes." Elliott Decl. at ¶ 49. Ambry thus admittedly uses probes that hybridize to a wild-type BRCA1 allele and thus Ambry's large rearrangement testing falls within the scope of claim 7, even as interpreted by Ambry.

Ambry's noninfringement argument in regard to '441 patent claim 7 and '857 patent claim 4 is likewise based on an erroneous claim construction. Ambry asserts that the reference to "BRCA1 gene" and "BRCA2 gene" in those claims "requir[es] that the entire genes (including all of the introns and exons) are screened." Ambry then asserts that "Plaintiffs have not demonstrated that [Ambry's] large rearrangement tests ... screen for rearrangements in all portions of the BRCA1 and BRCA2 genes." Defs' Opp. at 87.

However, the claim terms "BRCA1 gene" and "BRCA2 gene" are not limited in the manner that Ambry asserts. The patents expressly define both terms to include fragments and portions of each gene. The '441 patent defines the term "BRCA1 Gene" as "polynucleotides, all of which are in the BRCA1 region." '441 patent at col. 19, lines 30-32. That definition makes clear that the term means some number of nucleotides "in the BRCA1 region," not that every nucleotide in that gene must always be included. The specification continues, stating that "[t]hese terms, when applied to a nucleic acid, refer to a nucleic acid which encodes a BRCA1 polypeptide ***[or] fragment***," and that "[t]he nucleic acids of the present invention will possess a

sequence which is either derived from, or substantially similar to a natural BRCA1-encoding gene or one having substantial homology with a natural BRCA1-encoding gene ***or a portion thereof***." *Id.* at col. 19, lines 45-52 (emphasis added). The patent also states that, "[a]s used herein, a 'portion' of the BRCA1 locus or region or allele is defined as having a minimal size of at least about eight nucleotides, or preferably about 15 nucleotides," and similarly states that "[t]he DNA sequences used in this invention will usually comprise at least about five codons (15 nucleotides)." *Id.* at col. 20, line 66 to col. 21, line 1; col. 20, lines 37-38. The '857 patent defines the term "BRCA2 Gene" precisely the same way using exactly the same language except that it refers to BRCA2. '857 patent at col. 18, lines 14-16, 28-35; col. 19, lines 50-52, 21-22.

Ambry's attempt to restrict these claims in the '441 patent and '857 patent has no basis. Ambry's noninfringement argument thus fails, and Myriad is likely to succeed in proving infringement of these claims against Ambry.[27]

6. Defendants' Remaining General Arguments Relating to Infringement Likewise Lack Merit.

Otherwise, Ambry and Gene By Gene incorrectly argue in passing that Myriad's proof of infringement somehow lacks "specific evidence," but instead "generally characterize[s] the accused products" and supposedly includes "speculations about Defendants' tests and the technology at issue." Defs' Opp. at 76-77, 82, 85. To the contrary, Myriad provided specific evidence from Defendants' own documents for each element of the claims at issue. Plfs' Mot. at 16-30. Although Defendants provide declarations with descriptions of their tests, those descriptions are fully consistent with the description in Myriad's motion and, at most, merely

[27] Based on its current knowledge that GBG does not plan to perform large rearrangement analysis in the near future, Myriad's motion did not assert these claims against GBG. *See* Plfs' GBG at 18-26; Plfs' Ambry Mot. at 27-30. Defendants' reference in its opposition at page 87 to the GBG's declarant's statement about GBG's lack of intent in that regard (Mittleman Decl. at ¶ 21), is thus irrelevant.

provide additional details that do not alter the ultimate conclusion of infringement. *Compare* Plfs' Ambry Mot. at 16-30 *with* Elliott Decl. [Dkt #47] at ¶¶ 4-16; *compare* Plfs' GBG Mot. at 16-26 *with* Mittelman Decl. [Dkt #50] at ¶¶ 13-22. Critically, Defendants do not dispute any of Myriad's evidence or Myriad's description of Defendants' tests and underlying activities. Defs' Opp. at 76-87. In particular, Ambry's description refers only to the same documentation that Myriad submitted to prove infringement, while Gene By Gene's description refers to no documentation of any kind. Elliott Decl. at ¶¶ 9, 15, 20, 31; Mittelman Decl. at ¶¶ 13-22.

Finally, Defendants incorrectly assert that an injunction relating to the patent claims for "methods" is improper because Defendants have not yet performed the methods, they have merely "offered to sell" or "announced … intentions to sell" tests that will involve performing those methods. Defs' Opp. at 82-83. Defendants cite no case holding that an injunction is not appropriate under the circumstances. *See id.* Indeed, courts have held precisely the opposite. Where, as here, the patent owner is faced with "a viable threat of serious harm which cannot be undone," a preliminary injunction is appropriate. *S.J. Stile Associates Ltd. v. Snyder*, 646 F.2d 522, 525 (C.C.P.A. 1981). Unlike here, a preliminary injunction is inappropriate only if it is based on the "mere apprehension of potential future infringement" or merely "rumors of a threat of infringement." *Roper Corp. v. Litton Sys., Inc.*, 757 F.2d 1266, 1273 (Fed. Cir. 1985).

Moreover, Defendants' assertions in this regard contradict assertions made in the balance of the harms and public interest sections of their opposition, and the averments of their damages expert Scott Hampton. Mr. Hampton's declaration references a Gene by Gene press release representing that it has "processed testing for the BRCA1 and BRCA2 genes for individuals living outside the U.S. since 2012 … using traditional Sanger DNA sequencing … at the company's Genomic Research Center in Houston." Hampton Decl. at ¶ 20. And Ambry

publicly claims to have performed at least 1,000 BRCA tests. http://www.ambrygen.com/brca-beyond. Indeed, one can legitimately question how Ambry can claim to have an identifiable and purportedly improving VUS rate on BRCA1 and BRCA2 testing (*see* Defs' Opp. at 105), or how "Gene by Gene's BRCA1/2 test" can be said to be "extremely accurate and [of] high quality" (*id.* at 107), if Defendants have only "offered to sell" or "announced … intentions to sell" such tests. *Id.* at 82.

D. Defendants Have Failed to Raise a Substantial Question that the Asserted Primer Claims Are Invalid for Obviousness.

1. Legal Standards for Anticipation.

To establish anticipation Defendants must prove, by clear and convincing evidence, that the "four corners of a single, prior art document describe every element of the claimed invention," either expressly or inherently. *See, e.g., Xerox Corp. v. 3Com Corp.*, 458 F.3d 1310, 1322 (Fed. Cir. 2006). If a limitation is not expressly disclosed in an allegedly anticipating prior art reference, the Defendants bear the burden of showing that the limitation is inherently disclosed by the reference. *Electro Med. Sys., S.A. v. Cooper Life Scis., Inc.*, 34 F.3d 1048, 1052 (Fed. Cir. 1994). To establish inherency, the anticipatory feature or result must be consistent, necessary, and inevitable, not simply possible or probable, and it should be clear that it would be so recognized by persons of ordinary skill. *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006).

The single prior art document must disclose all elements of a claimed invention "arranged as in the claim." *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008). The prior art document must also "enable" the practice of the claimed invention. *Elan Pharms., Inc. v. Mayo Found. for Med. Educ. and Research*, 346 F.3d 1051, 1054 (Fed. Cir.

2003) ("[T]he prior art reference must teach one of ordinary skill in the art to make or carry out the claimed invention without undue experimentation.") (internal quotation omitted).

Defendants also bear the burden of actually showing that an asserted reference is prior art as of the date asserted by Defendants. *Mahurkar v. C.R. Bard., Inc.*, 79 F.3d 1572, 1576 (Fed. Cir. 1996) ("By challenging the validity of the '155 patent, Bard bore the burden of persuasion by clear and convincing evidence on all issues relating to the status of the Cook catalog as prior art.") Because much of the prior art asserted here is asserted under Section 102(a) or 102(g) of the Patent Act, which depends on Defendants showing conception or invention before the Myriad inventors, it is possible for Myriad to ante-date that art and remove it from consideration. *Id.* at 1576-77. Moreover, for art asserted under § 102(g), defendants must show the date of prior invention with actual evidence, and may not simply presume it from, for example, a submission date of an article to a publication. *See Thomson S.A. v. Quixote Corp.*, 166 F.3d 1172, 1175 (Fed. Cir. 1999) (providing that a totality of the evidence, under a rule of reason analysis, must demonstrate that art is qualified under § 102(g)).

2. Claims 29 and 30 of the '492 Patent to Pairs of Primers Are Not Anticipated by the Schutte Article.

a. The Schutte Article Is Not Prior Art to the '492 Patent.

Claims 29 and 30 of the '492 patent require that the claimed pair of single-stranded DNA primers are "for determination of the nucleotide sequence of a BRCA2 gene by a polymerase chain reaction." Because, as Defendants concede, the BRCA2 gene was not known before the inventors' discovery, Schutte's primers could not possibly have been for this purpose. Recognizing this flaw in their position, Defendants attempt to avoid the issue by contending that this Court should simply ignore the implicated claim language, labeling that language merely as an "intended use." And while Defendants are incorrect, as explained in Section I(A)(2)(b)

below, the Court need not even resolve this dispute because, under Defendants' theory of the claims, the Schutte article is not prior art to the '492 patent and thus cannot anticipate as a matter of law.

Defendants assign December 18, 1995, as the priority date for claim 29, and January 11, 1996, as the priority date for claim 30. Setting aside whether these dates are accurate, because the Schutte article[28] was not published more than one year before either of these dates—it published on October 15, 1995—it does not constitute § 102(b) prior art (*i.e.*, it is not a "statutory bar") in any event. Rather, as Defendants assert, the Schutte article can only possibly be prior art under § 102(a) or 102(g).

As noted above, those two sections of the Patent Act—unlike the § 102(b) statutory bar—allow for the possibility that inventors like the Myriad inventors may ante-date those references or, as is commonly stated, "swear behind" them. They may do this by showing that, before the relevant date of the piece of § 102(a) or § 102(g) prior art, the inventors had conceived of the subject matter as contained in the prior art reference. If the inventors can do this, the references are no longer prior in time under § 102(a) and/or § 102(g) and thus, are no longer "prior art" and cannot be used to invalidate a patent. *In re Stempel*, 241 F.3d 755, 826 (C.C.P.A. 1957) ("In the case of a reference, it is fundamental that it is valid only for what it discloses and if the applicant establishes priority with respect to that disclosure, and there is no statutory bar, it is of no effect at all."); *Alcon Research Ltd. v. Barr Labs. Inc.*, 837 F. Supp. 2d 364, 388 (D. Del. 2011) (citing *Stempel* and holding that asserted reference was not prior art where inventor "had demonstrated conception and reduction to practice of at least as much of his invention" as the asserted

[28] The Schutte article is attached to the Gregory Declaration as Exhibit M.

reference showed); *Eli Lilly & Co. v. Sicor Pharms., Inc.*, 705 F. Supp. 2d 971, 995 (S.D. Ind. 2010) (same).

As demonstrated in the declaration of Brad Swedlund, that is exactly the case here. Even using Defendants' reading of the claims, the Myriad inventors had already conceived of the subject matter of the claims by any of the dates defendants assign to the Schutte article. Swedlund Decl. ¶¶ 3-9. Defendants contend that the October 15, 1995 Schutte article discloses two pairs of single-stranded DNA primers that are at least 15 nucleotides in length, and that synthesize part of the native DNA sequence of BRCA2 in PCR. But, as demonstrated in the Swedlund Declaration, at least by July 25, 1995, and consistent with Defendants' asserted scope of claim 29, Myriad scientists had "a pair of single-stranded DNA primers of at least 15 nucleotides in length"; "the sequence of [those] primers [were] isolated from human chromosome 13"; and "the use of [those] primers in a polymerase chain reaction result[ed] in the synthesis of DNA comprising all or at least 15 contiguous nucleotides of the BRCA2 gene." Swedlund Decl. ¶¶ 3-9; *see* '492 patent, claim 29. The nucleotide sequence synthesized by these primers in PCR include exon portions of what was ultimately discovered to be the native DNA sequence of BRCA2.

Accordingly, well before any date assigned to the Schutte article by Defendants, the '492 patent inventors had conceived of the same subject matter as the Schutte article. The Schutte article therefore does not qualify as prior art to the '492 patent and cannot anticipate claims 29 or 30 as a matter of law.

b. The Schutte Article Does Not Disclose the Use of a Pair of Single-Stranded DNA Primers "For Determining the Nucleotide Sequence of a BRCA2 Gene."

As noted above, asserted claims 29 and 30 of the '492 patent are directed to a pair of single-stranded DNA primers "for determination of the nucleotide sequence of a BRCA2 gene

by a polymerase chain reaction." Defendants, simply ignore this claim language. They instead assert only that the claims are invalid by the Schutte article's disclosure of a pair of primers that allegedly synthesize in PCR any short part of what was later discovered by the '492 patent inventors to be the BRCA2 gene. Defendants' expert declarations attempt to set aside this plain language in the claims as just an "intended use," not a claim limitation, and perform no analysis of whether the Schutte article discloses that feature. *See* Gregory Dec., App'x 1 at 31-32. Contrary to Defendants' argument, the language that the primers must be "for determination of the nucleotide sequence" of the BRCA2 gene is a limitation of these claims, and the absence of that feature from the Schutte art is fatal. Defendants' anticipation analysis of these claims is thus deficient, and Defendants cannot raise a "substantial question" on anticipation by ignoring this basic and important claim language.

The claim language requiring DNA primers "for determination of a nucleotide sequence" of a BRCA2 gene appears in the preamble of claims 29 and 30 of the '282 patent. Language in a claim preamble serves to limit a claim "if it recites essential structure or steps, or if it is 'necessary to give life, meaning, and vitality' to the claim." *Vizio, Inc. v. Int'l Trade Comm'n*, 605 F.3d 1330, 1340-41 (Fed. Cir. 2010). Moreover, a preamble also serves to limit a claim where limitations in the body of the claim derive antecedent basis, *i.e.*, relate or refer back to, the preamble. *Highmark, Inc. v. Allcare Health Mgmt. Sys., Inc.*, 687 F.3d 1300, 1311-12 (Fed. Cir. 2012).

Here, the preamble provides life and meaning for the claim body and is critical to the purpose of the invention. The preamble provides the framework and context for the body of the claim because the preamble refers to primers for determining the sequence of a BRCA2 gene, and the claim body then refers back to the preamble as explaining that the use of those primers

results in synthesis of DNA with at least part of that BRCA2 nucleotides such that those nucleotides can be sequenced. *See Griffin v. Bertina*, 285 F.3d 1029, 1033 (Fed. Cir. 2002) (finding that preamble directed to "diagnosing an increased risk for thrombosis of a genetic defect causing thrombosis" was limiting where body of the claim also recited "wherein the presence of said point mutation in said test nucleic acid indicates an increased risk for thrombosis or a genetic defect causing thrombosis"). The preamble also provides antecedent basis for a limitation in the body of the claims, further demonstrating that they are intended to limit the claims. In claim 29 of the '492 patent, the preamble language "nucleotide sequence of a BRCA2 gene" provides antecedent basis for the term "the BRCA2 gene" that appears in the body of the claim and thus refers back to the prior use of the term. Accordingly, the preamble of claim 29 is a limitation and must be considered in the validity analysis.

Neither Defendants nor their experts even attempt to show that the Schutte article discloses primers "for determination of the nucleotide sequence of a BRCA2 gene." Nor can they. The sequence of BRCA2 was ***not*** known before it was discovered by the inventors of the '492 patent. Kay Decl. ¶49-53. 85. Accordingly, it was not known before then whether the short sequences disclosed in the Schutte article would encode for any part of the sequence of the BRCA2 gene. Kay Decl. ¶85. Instead, the Schutte article is directed only to general maps of the region where BRAC2 was ultimately discovered by the inventors. Kay Decl. ¶83, 85. There is no suggestion in the Schutte article that the disclosed "primer" sequences could be used to amplify and synthesize the BRCA2 gene. *Id*.

In short, the claim language means what it says and, to anticipate, any asserted pair of primers must be for determination of a nucleotide sequence of a BRCA2 gene. The Schutte

article does not disclose primers consistent with this claim language. Defendants therefore have not shown a substantial question that Schutte anticipates claims 29 and 30 of the '492 patent.

c. The Schutte Article Does Not Disclose Primers That Result in Synthesizing All or Part of the BRCA2 cDNA Sequence As Required by Claim 30.

Claim 30 depends from claim 29, and further specifies that "said BRCA2 gene has the nucleotide sequence set forth in SEQ ID NO:1." Importantly, the nucleotide sequence of SEQ ID NO:1 is the cDNA sequence of BRCA2, meaning that it contains only the exons of the BRCA2 DNA sequence. Kay Decl. ¶86. Accordingly, to anticipate claim 30, the Schutte article must disclose a pair of single-stranded DNA primers as described in claim 29 that, when used in a PCR reaction, result in the synthesis of a nucleic acid having all or at least 15 contiguous nucleotides of the BRCA2 cDNA (*i.e.*, SEQ ID NO:1) as opposed to a nucleic acid that includes any part of any introns from BRCA2. In other words, to anticipate, the pair of primers disclosed in the Schutte article must be complementary to the BRCA2 DNA sequence in a manner that results in amplification of at least 15 contiguous nucleotides of an exonic portion of the BRCA2 gene, which is reflected in SEQ ID NO:1, and cannot result in amplification of any nucleotides from any intronic portions of the BRCA2 gene because those intronic portions are not present in BRCA2 cDNA.

As Defendants admit, both of the primers in the 866s186 pair disclosed by Schutte hybridize within a single intron of what was later identified as the BRCA2 gene sequence. Defs' Opp. at 58. This necessarily means that those primers would result in the amplification of only intronic nucleotides. That fact is fatal to Defendants' anticipation argument because SEQ ID NO:1 does not contain the introns of the BRCA2 gene sequence. As such, the pair of "886s186" primers in the Schutte article cannot hybridize with any part of the nucleotide sequence of SEQ

ID NO:1, and therefore would not result in the synthesis of any contiguous nucleotides of SEQ ID NO:1. The "866s186" primer pair thus does not anticipate claim 30.

Further, with regard Schutte's "866s239" primer pair, Defendants admit that one primer hybridizes within an intron of BRCA2, and the other hybridizes within an exon of BRCA2. Defs' Opp. at 58. Accordingly, this pair of primers does not meet the limitations of claim 30 because it would result in the amplification of some intronic nucleotides, and thus would not result in an amplification product that excludes any intronic nucleotides. The "866s239" primer pair thus does not anticipate claim 30.

3. Claims 16 and 17 of the '282 Patent Are Not Anticipated by Abel, Anderson or the D17S855 and D17S932 Marker Deposits.

Turning to the other primer patent, Defendants have not raised a substantial question that each and every limitation of claims 16 and 17 of the '282 patent are disclosed in either the Abel or Anderson references, or the D17S855 and D17S932 database deposits.[29]

a. None of Abel, Anderson, or the Deposits Discloses "Primers For Determining the Nucleotide Sequence of a BRCA1 Gene" as Required by Claims 16 and 17.

As in claims 29 and 30 of the '492 patent, claims 16 and 17 of the '282 patent recite a pair of single-stranded DNA primers "for determination of a nucleotide sequence of a BRCA1 gene by polymerase chain reaction." And, just as with claims 29 and 30, Defendants ignore that claims 16 and 17 recite this language, instead asserting that the claims are invalid by disclosure of a pair of primers that allegedly synthesize a short part of what Myriad later determined to be the BRCA1 gene.

[29] These references were each attached as Exhibits to the Declaration of Dr. Gregory: Abel (Ex. A): Anderson (Ex. B); D17S932 (Ex. C).

For the same reasons discussed above, this language in claims 16 and 17 is limiting and precludes Defendants' anticipation argument. The Anderson and Abel articles, and the marker deposits, cannot possibly disclose pairs of primers "for determination of [all or part of] a nucleotide sequence of a BRCA1 gene by polymerase chain reaction," because the sequence of BRCA1 was ***not known*** before the invention of the '282 patent. Kay Decl. ¶38-48, 75. That art is merely directed to general maps of the regions that were merely hypothesized at the time to correspond to the BRCA1 gene. Kay Decl. ¶72-73. They thus do not disclose all the limitations of claims 16 and 17 and do not anticipate either of them. As with the prior claims, Defendants cannot raise a "substantial question" of anticipation by ignoring important claim language.

b. <u>The Marker Deposits Are Not "A Pair of Single-Stranded DNA Primers," As Required by Claims 16 and 17.</u>

Defendants also wrongly argue that each of the allegedly publicly accessible genetic markers D17S855 and D17S932 anticipates claims 16 and 17 of the '282 patent. First, neither marker constitutes "a pair of single-stranded DNA primers." When used in the context of PCR, one of ordinary skill in the art would understand a "pair of single-stranded DNA primers" to refer to a pair of single strands of DNA that are not fully complementary. Kay Decl. ¶29-37. Here, each of the markers asserted by Defendants is ***one double-stranded*** DNA fragment, not a pair of single-stranded DNA primers. Moreover, because they are double-stranded DNA, each of the markers includes strands of DNA that are fully complementary to each other. Thus, the marker deposits cannot function as and do not disclose "a pair of single stranded DNA primers."

Second, Defendants' scientifically erroneous suggestion that either marker's double-stranded DNA fragment can be separated in two and subsequently used as a single-stranded primer pair in PCR to amplify part of the BRCA1 gene should carry no weight. Defs' Opp. at 57. PCR involves using a pair of single-stranded primers that are ***not*** complementary to one

another to amplify target DNA located between the primers. Kay Decl. ¶29-30, 80. The result is an amplified PCR product that is double-stranded and incorporates the sequence of the first primer (forward primer) followed by the amplified target sequence, and further followed by the sequence of the second primer (reverse primer). Kay Decl. ¶31-37, 80. The 3' ends of the two primers used in a PCR reaction are, relative to the target DNA to be amplified, separated by a stretch of nucleotides ("target DNA") that is not found in either primer. *Id.* In other words, in PCR, the primers are used to amplify the target DNA, which is not part of the sequence of the primers used in the reaction. *Id.*

If, as Defendants posit, the double-stranded DNA fragment of the D17S855 or D17S932 markers were split into two single DNA strands, the single strands would neither function as, nor fit within the commonly understood meaning of a pair of primers for PCR. Kay Decl. ¶81. Rather, because those two DNA strands are complementary to one another, they would either exactly align and re-anneal to one another, or anneal to the exact same position along template DNA. *Id.* In either case, there would be no target DNA located between them to amplify. *Id.* Further, were the deposited markers used as a pair of "primers" in an attempt to perform PCR—and Defendants have not shown that they ever were—no double-stranded, amplified PCR product having the sequence of the first primer followed by the amplified target sequence followed by the second primer would be produced.

Simply put, double-stranded DNA fragments like the asserted marker deposits are not single-stranded primer pairs and cannot be used in PCR to synthesize all or part of the BRCA1 gene as claimed. Claims 16 and 17 of the '282 patent thus are not anticipated by the marker deposits for this additional reason.

c. Neither Abel, Anderson Nor the Marker Deposits Disclose Primers That Result in Synthesizing All or Part of the BRCA1 cDNA Sequence (SEQ ID NO:1) As Required by Claim 17.

In addition to the requirements noted above that apply to both Claims 16 and 17, dependent claim 17 further specifies that "said BRCA1 gene has the nucleotide sequence set forth in SEQ ID NO:1." Thus, to anticipate claim 17, Abel, Anderson, and the marker deposits must disclose a pair of single-stranded DNA primers that, when used in a PCR reaction, results in the synthesis of DNA having all or part of the sequence of SEQ ID NO:1. SEQ ID NO:1 reflects the cDNA sequence of the BRCA1 gene; that is, it contains only the exon portions of the gene and no intron portions. Kay Decl. ¶68. None of these references discloses a pair of primers that would synthesize a nucleic acid comprising any part of a BRCA1 exon in a PCR reaction, let alone such a nucleic acid that has no intronic nucleotides. Consequently, none of these references anticipates claim 17.

The Abel and Anderson articles both disclose the same set of primers that are complementary to only previously unknown and undefined intron regions of the BRCA1 genomic DNA sequence, and not to any exon portions. Kay Decl. ¶76, Ex. H. Thus, if the Abel/Anderson primers can be used in PCR to synthesize anything, they would aid in the synthesis of a nucleic acid having an exclusively intronic sequence. Because the cDNA of SEQ ID NO:1 does not contain the intron portions of the BRCA1 gene, the Abel and Anderson primers cannot and do not hybridize to any part of—let alone all of—SEQ ID NO:1, and cannot and do not produce a PCR synthesis product comprising all or part of the sequence of SEQ ID NO:1.

Likewise, markers D17S855 and D17S932 fall entirely within an intron portion of the BRCA1 gene, and do not extend into any exon portion. Kay Decl. ¶79, Ex. H. Accordingly, the markers cannot and do not hybridize to any sequence of SEQ ID NO:1, and cannot and do not

produce a PCR synthesis product having all or part of the sequence of SEQ ID NO:1. In fact, as described above, the markers are coextensive and if used in PCR would not result in any amplified PCR product having the sequence of the first primer, followed by the amplified target sequence, followed by the second primer.

d. The Work Underlying the Anderson and Abel Articles Cannot Invalidate Claims 16 and 17 Under 35 U.S.C. § 102(g).

Defendants assert that the work leading up to the submission of the Abel and Anderson article qualifies as prior art under 35 U.S.C. § 102(g), because the authors actually invented the subject matter of claims 16 and 17 no later than when the articles were submitted to their respective journals on December 28, 1992, and therefore before the named inventors of the '282 patent. Defendants, however, offer no evidence that the contents of the published Abel and Anderson articles reflects what the authors actually submitted for publication on December 28, 1992. In fact, at least the Anderson article indicates that it was revised once, on March 19, 1993, so it is unclear whether, as submitted, it contained the primer pair Defendants rely on for anticipation.

Indeed, it is common for articles to be revised during the review process. Kay Decl. ¶5. Often reviewers require the authors to perform additional experiments to generate more data to include in the manuscript before publication. Kay Decl. ¶5. Defendants simply have not shown if and when, before publication, the authors of the Abel and Anderson allegedly invented the subject matter of claims 16 and 17. As a result, the Abel and Anderson articles cannot be used to invalidate claims 16 and 17 of the '282 patent under 35 U.S.C. § 102(g)(2). *Teva Pharm. Indus. Ltd. v. AstraZeneca Pharms. LP*, 661 F.3d 1378, 1383 (Fed. Cir. 2011) (to establish prior invention, defendants must show either that another inventor reduced the invention to practice

first, or that another inventor was the first party to conceive of the invention and then exercised reasonable diligence in reducing that invention to practice).

E. Defendants Have Not Shown that the Asserted Method Claims Are Likely To Be Found Invalid As Obvious.

For the remaining claims asserted in Myriad's preliminary injunction motion—the method claims—Defendants concede that none is anticipated.[30] Defendants must do so because there can be no question that the BRCA1 and BRCA2 sequences recited in the claims of the '441 patent and '857 patent were not known at the time of the inventions; they were discovered by Myriad. Likewise, there is no question that the consensus sequences claimed in the '155 and '721 patents were not known in the art; they, again, were discovered by the named inventors on those patents.

Because these key elements of the claims were not known, Defendants can only argue that techniques used to discover genes generally were known, and point the Court to prior art that was fully considered (and rejected) by the Patent Office, in a strained effort to argue that the widely-hailed discoveries contained in these patents were somehow "obvious" to persons of ordinary skill in the art. But, under the correct legal framework for obviousness, Defendants have not come close to meeting their burden to show they have raised a substantial issue of obviousness. Instead, the inventions at issue were exactly the "revolutionary" discoveries they were portrayed to be at the time of their invention.

[30] In their brief, Defendants argue only that the asserted method claims are obvious. (Defs' Opp. at 59 ("Plaintiffs' Asserted Method Claims are Obvious Under Section 103").) In his declaration, Defendants' expert, Dr. Gregory, sets forth additional obviousness arguments and also asserts that the method claims are anticipated. Because these arguments are not in Defendants' brief, Myriad does not address those arguments here, but addressed them through the declaration of Dr. Kay.

1. Legal Standards for Obviousness.

A determination of obviousness under 35 U.S.C. § 103 is a legal determination based on four factual inquiries: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence, or secondary considerations, of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *In re Cyclobenzaprine*, 676 F.3d 1063, 1068 (Fed. Cir. 2012). Objective evidence probative of non-obviousness includes copying, commercial success, failure of others, long-felt need, general skepticism of those in the art, and unexpected results. *See KSR*, 550 U.S. 398, 406 (2007). Obviousness is analyzed from the perspective of one of skill in the art at the time of the invention—the use of hindsight is not permitted. *See KSR*, 550 U.S. at 421 (recognizing "hindsight bias" and "ex post reasoning" as inappropriate in determination of obviousness).

A party seeking to invalidate a patent based on obviousness must demonstrate by clear and convincing evidence that a person skilled in the art (1) "would have been motivated to combine the teachings of the prior art references to achieve the claimed invention," and (2) "that the skilled artisan would have had a reasonable expectation of success in doing so." *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009). While in some situations a claim may be obvious if it is "obvious to try," this is only true where there were a "finite number of identified, predictable solutions." *KSR*, 550 U.S. at 421; *see also* 35 U.S.C. § 103 ("Patentability shall not be negated by the manner in which the invention was made.").

2. Claims 7 and 8 of the '441 Patent Are Not Obvious Because The Discovery of the BRCA1 Gene Was Not Obvious.

Claims 7 and 8 of the '441 patent each depend from claim 1, which provides a method for screening the germline (genetic material capable of being passed on to offspring) of a human subject for alterations of the BRCA1 gene. Defendants concede that the sequence of the BRCA1

gene was not known at the time of the invention of claims 7 and 8 of the '441 patent. Claims 7 and 8 thus cannot be anticipated.[31] Undeterred, and without citation to any prior art except "the state of the art," Defendants and their experts assert that any scientist could have identified the BRCA1 gene using certain "tools" and "techniques" known in the art.

Defendants' argument not only defies common sense and runs afoul of established Federal Circuit law, but would improperly render obvious nearly every invention made using known tools and methods. That is not the law.

a. <u>The Inventors Did Not Face a "Finite Number of Predictable Solutions" in Searching for the BRCA1 Gene.</u>

At the time of the invention, those of skill in the art had determined that the human BRCA1 gene was likely responsible for a large proportion of familial breast and ovarian cancer cases. Kay Decl. ¶38. It was also understood that the BRCA1 gene was linked to chromosome 17q21. *Id*. However, because the biochemical effects underlying inherited human breast cancer were unknown, those of ordinary skill in the art had to identify the responsible gene without the benefit of its protein product. Kay Decl. ¶40. This meant that the gene had to be identified using "positional cloning" techniques, which rely upon "linkage analyses" to familial data to search for the location of the disease-causing gene. Kay Decl. ¶40.

At the time of the invention, the person of ordinary skill in the art faced many choices when using positional cloning techniques to search for the BCA1 gene, and wrong choices could

[31] In a footnote, Defendants assert that claim 8 (but not claim 7) is anticipated by a 1993 article by Bowcock. Defs' Opp. at 70, n.16. That article cannot anticipate claim 8 at least because it does not disclose the wild-type sequence of the BRCA1 gene. Kay Decl. ¶117. Thus, even if Bowcock 1993 disclosed a method for isolating the BRCA1 gene (which it does not), it could not anticipate claim 8, which requires a comparison of a BRCA1 gene isolated from a subject with the wild-type BRCA1 sequence. Kay Decl. ¶113, 115, 117.

easily have led to failure. As detailed below, the inventors followed an unconventional path to successfully discover the BRCA1 gene where others failed.

(1) At the Time of the Invention, There Was a Great Deal of Uncertainty Regarding the Region Where the BRCA1 Gene Might Be Located.

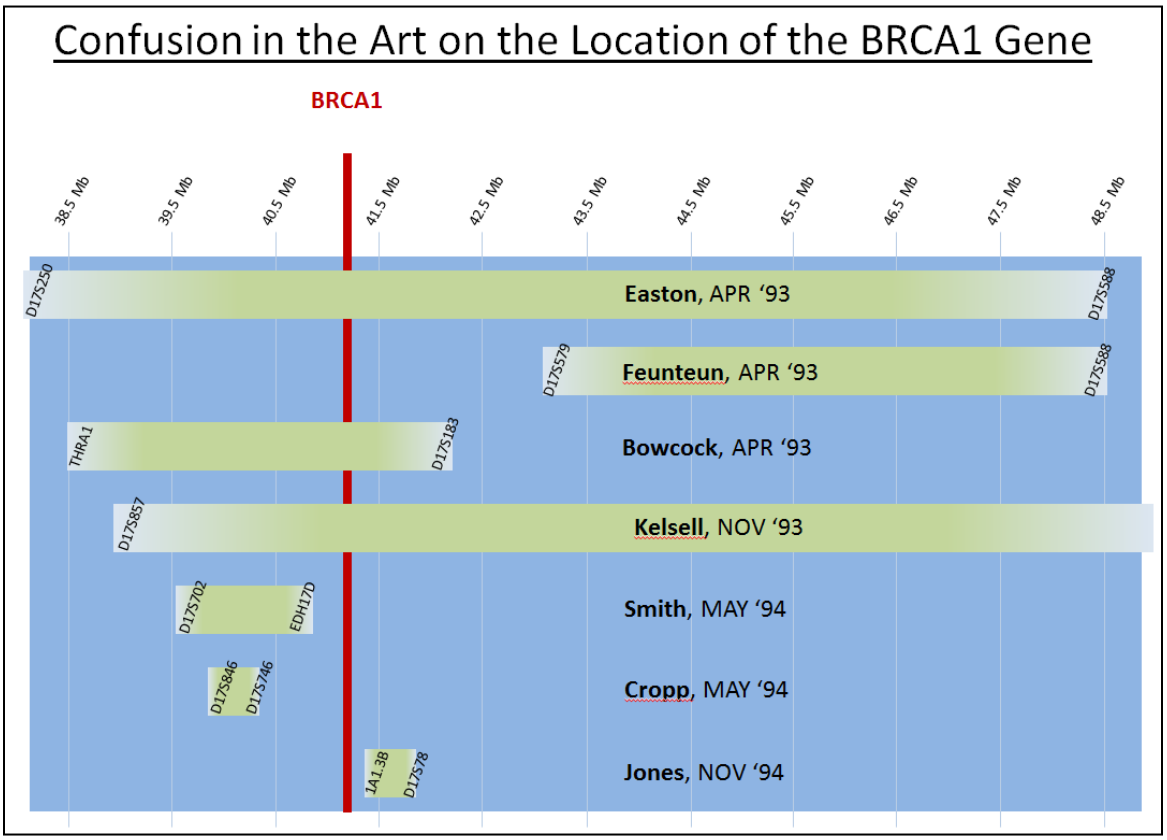
Faced with the problem of trying to find the BRCA1 gene, the ordinarily skilled artisan would first have to choose a region of chromosome 17q21 in which to begin their search. Kay Decl. ¶93-106 But, at the time of the invention, there was great uncertainty in the art and numerous competing theories regarding where on chromosome 17q21 the BRCA1 gene ***might*** even potentially be located.

In April 1993, an article published by Easton reported that the BRCA1 gene might be found in a region that spanned approximately **8.3 million** base pairs in men and **18 million** base pairs in women. Kay Decl. ¶94; Gregory Decl., Ex. U at 402. Also in April 1993, an article published by Feunten suggested that the breast-ovarian cancer locus could be found in a region of greater than **four million** base pairs that overlapped with the region disclosed in Easton, but ultimately was found not to include the BRCA1 gene. Kay Decl. ¶ 84, Ex. I at 736. Also in April 1993, an article published by Bowcock, and relied on by Defendants, indicated that the BRCA1 gene might be found in another region of nearly **four million** base pairs that did not overlap in any way with the region identified in the Feunten article. Kay Decl. ¶95; Gregory Decl., Ex. V at 718. At the end of 1993, an article published by Kelsell posited that the BRCA1 gene might be found anywhere distal of a marker located at the far end of the region identified by Bowcock. Kay Decl. ¶96; Gregory Decl., Ex. E at 1823.

In 1994, there continued to be confusion regarding the potential location of the BRCA1 gene. A 1994 article by Smith identified an interval of around one million base pairs as the likely location for the BRCA1 gene, but that region did not end up including the BRCA1 gene.

Kay Decl. ¶97; Kay Decl., Ex. J at 71 A 1994 article by Cropp suggested that BRCA1 may fall within an entirely separate region of less than 100,000 base pairs but, again, it was eventually discovered that that region did not contain the BRCA1 gene. Kay Decl. ¶98, Ex. K at 2549.

Indeed, even after Myriad discovered the BRCA1 gene and filed its patent application, other entities were **still** publishing papers demonstrating the confusion that existed regarding the potential location of the BRCA1 gene. In November 1994, several months after Myriad filed the patent application that led to the '441 patent, Jones published an article suggesting that BRCA1 lay in yet a different region of chromosome 17 that did not contain the BRCA1 gene. Kay Decl. 101, Ex. L at 1927. In short, as shown in the figure below and looking at the prior art as a whole, there was no consensus at the time of the invention regarding the region where the BRCA1 gene even ***might*** be located:



Defendants incorrectly assert that a person of ordinary skill in the art would immediately be drawn to the ranges identified by the Bowcock and Kelsell articles instead of the ranges identified by the other references, several of which post-date Bowcock and Kelsell. In selecting a region to search for the BRCA1 gene, the ordinarily skilled artisan could have selected any of the above regions, most of which we now know would have led (and for many did lead) to a dead end in that search. Kay Decl. ¶100, 102. In ignoring these references, Defendants focus on the region where the BRCA1 gene was ultimately discovered (even though many skilled artisans at the time did not) for no apparent reason other than they now know (because of Myriad's discovery) that the BRCA1 gene is located in that region. The Federal Circuit has routinely warned against such an approach. *See Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1379 (Fed. Cir. 2012) ("[T]he proper analysis requires a form of amnesia that 'forgets' the invention and analyzes the prior art and understanding of the problem at the date of invention."); *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012) ("The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight. What matters is the path that the person of ordinary skill in the art would have followed."). Said another way, Defendants' arguments are hindsight, plain and simple. *See Graham*, 383 U.S. at 36 (discussing the "importance of guard[ing] against slipping into the use of hindsight ... and resist[ing] the temptation to read into the prior art the teachings of the invention in issue" when considering the obviousness of a patent); *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1209 (Fed. Cir. 1991) ("Hindsight is not a justifiable basis on which to find that ultimate achievement of a long sought and difficult scientific goal was obvious".).

In addition to postulating different views on the location of the BRCA1 gene, many in the field had already identified possible candidate genes for BRCA1. For example, in 1990 Dr. King

identified 17-β hydroxysteroid dehydrogenase as a "most biologically plausible candidate gene," but it did not turn out to be BRCA1. Gregory Decl., Ex. F at 89. Also in 1990, Hall identified several plausible candidate genes. Gregory Decl., Ex. H at 1688-89. In 1992, Hall again identified several "plausible candidate genes," none of which turned out to be BRCA1. Gregory Decl., Ex. I at 1240, 1242. Before even venturing to explore the large regions identified by papers such as Bowcock, Feunten, or Kelsell, persons of ordinary skill in the art may have simply investigated "plausible genes" identified by others to determine whether or not they were BRCA1. Kay Decl. ¶103-04 In fact, Dr. King herself took this approach and became frustrated when those candidates did not pan out. Kay Decl. ¶104; Mangum Decl., Ex. G at 224-25. Adding to the confusion, just two months before Myriad filed the application that led to the '441 patent, another set of investigators hypothesized that the 17HSDI "pseudogene" was a potential candidate for BRCA1. Kay Decl. ¶105; Kay Decl., Ex. M at 1327.

Simply stated, given the reports in the literature identifying varying regions where the BRCA1 gene might be located and candidate genes suitable for evaluation, the person of ordinary skill in the art was not faced with a "finite number of identified, predictable solutions" for discovering the BRCA1 gene. *KSR*, 550 U.S. at 421; *Cyclobenzaprine*, 676 F.3d at 1072 (explaining that evidence of obviousness "is insufficient unless it indicates that the possible options skilled artisans would have encountered were 'finite,' 'small,' or 'easily traversed,' and that skilled artisans would have had a reason to select the route that produced the claimed invention"); *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008) (explaining that, in unpredictable arts, "*KSR*'s focus on these 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable").

(2) Even Assuming a Correct Starting Point, One of Skill in the Art Could Have Followed Many Pathways in Search for the BRCA1 Gene.

Even if the skilled artisan selected a starting region of chromosome 17q21 that contained the BRCA1 gene—and as demonstrated above that would only have been done with hindsight—the ordinarily skilled artisan would have been faced with many potential pathways using positional cloning in the search for that gene. Positional cloning is a complex and uncertain method, and the fact that such techniques had worked for other genes does not lead to the conclusion that it will also work for another gene. Kay Decl. ¶106. Indeed as explained in Section I(B)(2)(b), there have been many attempts to clone genes using positional cloning techniques that have been unsuccessful. A review of the steps the inventors ultimately took to discovering BRCA1 demonstrates the complex nature of the techniques and the criticality of each decision made in the discovery process.

First, because they were starting with a range of millions of base pairs, the inventors had to use linkage analyses to narrow the range in which they would search for the BRCA1 gene. '441 patent at 4:22-25; 7:38-57; 9:21-47. Linkage analyses, while known, were highly unpredictable techniques in the early 1990s. Kay Decl. ¶106. In addition, linkage analyses relied heavily on the family data available to the group performing the analyses. Kay Decl. ¶41; Skolnick Decl.[32] ¶10; Shattuck Decl.[33] ¶¶9-14; '441 patent at 8:20-42. As a result of decades of work, Myriad had collected the largest and highest quality collection of population data available. Skolnick Decl. ¶¶4-12, '441 patent at 8:20-42. This information, which was not

[32] The Declaration of Dr. Mark Skolnick, submitted as Docket No. 172 in *Association for Molecular Pathology v. United States Patent and Trademark Office*, No. 09-Civ. 4515 (RWS) (S.D.N.Y.), is attached as Ex. D to the Declaration of Dr. Mark Kay.

[33] The Declaration of Dr. Donna Shattuck, submitted as Docket No. 171 in *Association for Molecular Pathology v. United States Patent and Trademark Office*, No. 09-Civ. 4515 (RWS) (S.D.N.Y.), is attached as Ex. C to the Declaration of Dr. Mark Kay.

available publicly, led the inventors to the region of chromosome 17q21 where they ultimately found the BRCA1 gene. Shattuck Decl. ¶¶9-14. Defendants have presented no evidence that publicly available family data would have necessarily led a person of ordinary skill in the art to the region that contained the BRCA1 gene through linkage analyses. Moreover, given the technology available in 1994, only a limited number of families could be comprehensively screened for mutations. Kay Decl. ¶¶41-42; Shattuck Decl. ¶¶15-16. The inventors made extremely important technical decisions related to choosing the right families to further narrow the target region for the BRCA1 gene, and Defendants have provided no evidence that a person of ordinary skill in the art would have made the same technical decisions. *Id.*

Second, once they narrowed their search region to a particular range through linkage analyses, the inventors took the unconventional step of using P1 and BAC clones to physically map that region of the gene, instead of the YAC clones that were preferred in the art. Shattuck Decl. ¶¶17-21. The literature at the time shows that YACs were the generally accepted means in candidate gene identification and that others searching for the BRCA1 gene touted the use of YACs and cosmids. Kay Decl. ¶¶ 110-11; Shattuck Decl. ¶¶17-21; Mangum Decl., Ex. H at 1017, and Ex. I at 6377-78. Indeed, even though Dr. Gregory opines that those of skill would have used P1 and BAC clones in addition to YAC clones, the very paper he cites as "teaching techniques and methods to identify BRCA1 Gene" focuses on YACs, and notes that P1 and BAC clones "have not been used extensively." Gregory Decl. ¶¶121-23; Gregory Decl., Ex. G at 127. Nonetheless, the inventors relied heavily on P1 and BAC clones because they believed they were more stable and manageable in size. Shattuck Decl. ¶20. It was later recognized that the structure of the BRCA1 region made YACs inherently unreliable, and the inventors' unconventional use of P1 and BAC clones led to their discovery of the BRCA1 gene. *Id.* at ¶21.

Indeed, Dr. Mary-Claire King proclaimed at a scientific conference after the inventors' discovery of the BRCA1 gene that "P1 and BACs are the winners of the day." Shattuck Decl. ¶20.

Third, the inventors developed and used a novel hybrid selection technique that increased hybridization efficiency and sensitivity. Shattuck Decl. ¶¶ 22-26. This modified hybridization technique proved to be the most effective method used in the search for candidate genes. *Id*.

Fourth, in attempting to physically map the narrowed BRCA1 region, the inventors needed luck and ingenuity to assemble the BRCA1 gene from segments of cDNA because of the large size of the gene and a long "open reading frame," which is a potential amino acid coding region located between a start signal and a stop signal. Kay Decl. ¶46 ; Shattuck Decl. ¶27. Because of its sheer size, the inventors could not have identified the full-length BRCA1 cDNA in a single clone and instead had to piece together non-overlapping gene cDNA fragments. Kay Decl. ¶46; Shattuck Decl. ¶ 29. If the inventors had incorrectly believed an incomplete open reading frame to be complete, or had made minor sequence errors in piecing together cDNA fragments, the BRCA1 gene may never have been discovered. Kay Decl. ¶ 46; Shattuck Decl. ¶¶ 27-29.

Finally, the inventors recognized the BRCA1 gene as the breast cancer susceptibility gene despite the absence of somatic mutations in sporadic breast cancer patients. Throughout the search for the BRCA1 gene, those in the field assumed that the gene encoded a classic tumor suppressor, which involve both familial and somatic cancers. Shattuck Decl. ¶30. The inventors did not find any somatic mutations in the studied breast and ovarian tumor cells. *Id*. ¶33. Although this caused some in the field to question whether the gene identified by the inventors was in fact BRCA1, the inventors ignored this "problem" and continued to pursue the gene that would eventually be identified as the BRCA1 gene. Shattuck Decl. ¶¶31-32.

Given all of the variables that the inventors faced, Defendants' claim that "by the start of 1994, it was clear to the field what steps and techniques would be employed in order to discover the location and sequence of the BRCA1 gene" is meritless. *In re Omeprazole Patent Litig.*, 536 F.3d 1361, 1380 (Fed. Cir. 2008) (affirming non-obviousness finding where "[t]he district court gave lengthy consideration to the multiple paths that would have faced a person of ordinary skill in the art who recognized" the problem solved by the patents). The prior art simply did not provide a finite number of identified, predictable solutions.

b. <u>There Was No Reasonable Expectation of Success that the BRCA1 Gene Would Be Identified and Isolated.</u>

For many of the same reasons set forth above, a person of ordinary skill in the art could not have had a reasonable expectation of success of discovering the location of the BRCA1 gene.

The art of positional cloning was very unpredictable in the early 1990s and in no way provided a reasonable expectation of success in discovering any particular gene. Kay Decl. ¶106. For instance, in the search for the disease-causing cystic fibrosis (CF) gene, a group of scientists used positional cloning techniques, based on linkage analyses, in their attempt to identify the disease-causing gene. Kay Decl. ¶106; Kay Decl., Ex. N. The group believed they discovered the CF gene and their work was published in *Nature*, one of the leading scientific journals. *Id*. More than a year later, however, it was discovered that the group's candidate gene was not related to CF. Kay Decl. ¶106; Kay Decl., Ex. O.

Even if the techniques available for positional cloning had not led to failures in the past, the Federal Circuit long ago rejected the premise that the discovery of DNA or cDNA could be obvious just because there are known methods to isolate such molecules, generally. *See In re Deuel*, 51 F.3d 1552, 1559 (Fed. Cir. 1995) ("Until the claimed molecules were actually isolated and purified, it would have been highly unlikely for one of ordinary skill in the art to

contemplate what was ultimately obtained. What cannot be contemplated or conceived cannot be obvious.").[34]

The prior art cited by Defendants also shows the unpredictability of the search for the BRCA1 gene. Indeed, those references demonstrate the uncertainty involved in the complex and unpredictable endeavor of searching for the BRCA1 gene. *See* Gregory Decl., Ex. V. Defendants' own expert, Dr. Bowcock, expressed concern about the accuracy and reliability of many of the techniques being used at the time for positional cloning. Kay Decl. ¶¶107-112; Gregory Decl., Ex. V. at 127-28, 131.

Defendants also cannot show there was a reasonable expectation of success just because many research groups were pursuing the gene or because of "the sizeable investment by Plaintiffs' corporate partners and the Federal Government." *See Cardiac Pacemakers, Inc. v. St. Jude Medical, Inc.*, 381 F.3d 1371, 1377 (Fed. Cir. 2004) ("Recognition of a need does not render obvious the achievement that meets that need."); *Innogenetics N.V. v. Abbott Labs.*, 512 F.3d 1363, 1373 (Fed. Cir. 2008) ("[K]nowledge of a problem and motivation to solve it are entirely different from motivation to combine particular references to reach the particular claimed [invention]."). Certainly, there were a large number of well-financed groups trying to find the gene linked to an increased risk of breast cancer. But, instead of evidencing a reasonable expectation of success, the massive effort to find this gene—and the time it took for the inventors to find it—shows just the opposite: that the inventors clearly made a tremendous discovery in identifying the BRCA1 gene.

[34] Nor did the Supreme Court in analyzing § 101 suggest that claims were obvious because the processes used to isolate DNA were known in the art. There was no obviousness claim before the Court. Moreover, in the sentence prior to the quote cropped by Defendants, the district court recognized that "the isolation of the BRCA1/2 genes required considerable effort on the part of Myriad and its collaborators as well as ingenuity in overcoming technical obstacles associated with the isolation process." *Association for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F. Supp. 2d 181, 202-203 (S.D.N.Y. 2010).

c. The Discovery of the BRCA1 Gene Was Not Obvious Under *Kubin* or *KSR*.

Defendants rely heavily on *In re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009), as purported support for their obviousness arguments, but the case is readily distinguishable. In *Kubin*, a claim to DNA (polynucleotides) encoding a protein was held obvious because the encoded protein had already been disclosed in the prior art, methods were known for obtaining the DNA sequence that encoded the protein, and a person of ordinary skill in the art would have been motivated to isolate the DNA sequence encoding the protein because the protein was considered valuable scientifically and would have had a reasonable expectation of success of doing so. *Id.* at 1360-61. Unlike *Kubin*, the proteins encoded by the BRCA1 gene were ***not*** known at the time of the inventions at issue here, and did not serve as the basis for working backward to obtain the DNA sequence encoding the protein. Kay Decl. ¶40. Rather, the BRCA1 gene was identified using a positional cloning approach that, based on the inventors' inventive choices and a bit of luck, allowed them to pinpoint the genes and obtain their DNA sequences. *Id.*

With the BRCA1 gene being unknown at the time of the inventions, *Kubin's* discussion of the use of "standard techniques" and "a finite number of identified, predictable solutions" is not relevant. Where the specific gene is not yet known, the existence of standard cloning or sequencing techniques does not suggest obviousness. *In re Bell*, 991 F.2d 781, 784-85 (Fed. Cir. 1993) (finding that human DNA sequences encoding IGF proteins were not obvious over references showing gene cloning method and complete amino acid sequences of IGFs). Indeed, as the Federal Circuit has explained, "[u]ntil the claimed molecules were actually isolated and purified, it would have been highly unlikely for one of ordinary skill in the art to contemplate what was ultimately obtained. What cannot be contemplated or conceived cannot be obvious." *In re Deuel*, 51 F.3d at 1559.

The claimed inventions are also not "obvious to try" under *KSR*. *KSR*, 550 U.S. at 421. The Federal Circuit has explained that there is no obviousness when "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988); *see also In re Cyclobenzaprine*, 676 F.3d at 1072. That is precisely the case here, where there existed a number of potential candidates for the BRCA1 gene in the general region that had been identified, and Defendants have cited to no reason why researchers would have focused on the area in which the inventors ultimately discovered contained the gene. The Court in *O'Farrell* also explained that an "obvious to try" analysis is impermissible where "what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *O'Farrell*, 853 F.2d at 903. Again, this is just the type of analysis that Defendants perform here, arguing that the inventions are obvious because the prior art provided some information as to the general region where the BRCA1 gene were located, even though they can cite to no specific guidance in the prior art as to how to identify the gene. In this type of situation, the invention is not obvious to try. *See Leo Pharm. Prods., Ltd. v. Rea*, ___ F.3d ___, 2013 WL 4054937 (Fed. Cir. Aug. 12, 2013) (finding that claimed invention was not obvious to try where prior art provided broad and general guidance as to various possibilities for a drug formulation but "[t]here [wa]s no indication in the prior art which of these possible formulations would be the most promising to try").

Moreover, even if Defendants could show that the claimed inventions were obvious to try, that is not enough. Defendants would still need to show that the inventions were obvious to try ***with a reasonable expectation of success***. *See In re Cyclobenzaprine*, 676 F.3d at 1070 ("While it may have been obvious to experiment with the use of the same PK profile when contemplating an extended-release formulation, there is nothing to indicate that a skilled artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective."); *In re Brimonidine Patent Litig.*, 643 F.3d 1366, 1376 (Fed. Cir. 2011) (rejecting Appellants' obvious to try argument where evidence supported that invention would not have been an "anticipated success"). As discussed in Section I(B)(2)(a)(i), Defendants have failed to show that a person of ordinary skill in the art would have any reasonable expectation of success in discovering the BRCA1 gene, or in conceiving of the subject matter of claims 7 and 8.

3. Claim 4 of the '857 Patent Is Not Obvious.

Claim 4 of the '857 patent depends from claim 2, which provides a method for diagnosing a predisposition for breast cancer in a human subject. The method of claim 2 requires the comparison of the germline sequence of the BRCA2 gene from a human subject to the wild-type sequence of the BRCA2 gene. Claim 4 further specifies the different types of assays that may be used to perform the comparison set forth in claim 2.

Like the BRCA1 gene in the context of the '441 patent, Defendants concede that the sequence of the BRCA2 gene was not known at the time of the invention of claim 4 of the '857 patent. Claim 4 thus cannot be anticipated. Once again, in their brief, Defendants rely on the "state of the art" to assert that a person of skill in the art could have routinely identified the BRCA2 gene. Indeed, Defendants devote only two conclusory sentences in their brief toward

the supposed "obviousness" of discovering the BRCA2 gene. Defs' Opp. at 72. As with the BRCA1 gene, Defendants have failed to raise a substantial question of obviousness.

a. <u>As They Did with the BRCA1 Gene, the Inventors Followed an Unconventional Path to Identify the BRCA2 Gene.</u>

The '857 patent explains that the search for the BRCA2 gene involved a similar approach to that described above for the identification of the BRCA1 gene. '857 patent at 6:60-15:67; Tavtigian Decl. ¶4.[35] At the start of their search, the inventors focused on a region of six million base pairs in human chromosome 13 that they believed might contain the BRCA2 gene. '857 at 6:62-67. The inventors then performed linkage analyses using data from 19 families with multiple members affected by breast cancer to identify a region of 1.5 million base pairs where they thought the BRCA2 gene might be located. '857 patent at 34:19-36:60, tbl.1. The inventors were then able to construct a physical map of cloned DNA covering the identified region using a combination of yeast artificial chromosomes and other DNA cloning vectors. '857 patent at 36:61-37:3, fig.1; *see also* Shattuck Decl. ¶ 17.

Once they had cloned the region, the inventors used a range of challenging gene discovery techniques to identify genes in that region. '857 patent at 37:34-44:5. The inventors analyzed thousands of clones containing fragments of BRCA2 candidate genes for sequence changes that could adversely affect the function of a protein coded for by that candidate gene fragment. '857 patent at 39:51-40:37. After they identified the region that they believed was the BRCA2 gene, the inventors identified mutations that segregated with familial breast cancer in nine of the eighteen families screened. *Id.* at col. 46:48-67, tbl.3. These studies provided

[35] The Declaration of Dr. Sean Tavtigian, submitted as Docket No. 174 in *Association for Molecular Pathology v. United States Patent and Trademark Office*, No. 09-Civ. 4515 (RWS) (S.D.N.Y.), is attached as Ex. E to the Declaration of Dr. Mark Kay.

convincing evidence that the inventors had identified BRCA2, the gene responsible for familial breast cancer on chromosome 13.

In finding the BRCA2 gene, the inventors faced nearly all of the same difficulties and were forced to make the same technical decisions that they made in uncovering the BRCA1 gene. For instance, the inventors again had access to a large and quality set of familial data (not available to the public) that helped them to successfully narrow the region where the BRCA2 gene was located on chromosome 13. Kay Decl. ¶¶49-53. The inventors further had to make difficult technical decisions regarding what families to focus on in performing their search. *Id*. As with the BRCA1 gene, the inventors used the unconventional BAC and P1 cloning techniques, as well as their novel hybridization technique, to help them successfully identify the BRCA2 gene. *Id*. And, finally, because the BRCA2 gene is unusually large (it is composed of 3418 amino acids) and bore no significant sequence similarities to other known proteins, the inventors had to use ingenuity and needed a bit of luck to successfully assemble a complete sequence from cDNA clones. *Id*.

As with the BRCA1 gene, the inventors' path to BRCA2 itself demonstrates that the person of ordinary skill in the art was not faced with a "finite number of identified, predictable solutions" in the search for the BRCA2 gene. *KSR*, 550 U.S. at 421; *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008) ("*KSR* posits a situation with a finite, and in the context of the art, small or easily traversed, number of options that would convince an ordinarily skilled artisan of obviousness. …. [T]his clearly is not the easily traversed, small and finite number of alternatives that KSR suggested might support an inference of obviousness.").

b. Instead of Rendering Claim 4 of the '857 Patent Obvious, Wooster (1995) Shows Exactly Why the Discovery of the BRCA2 Gene Was Not Obvious.

Defendants' opposition does not identify any specific prior art references that allegedly render claim 4 obvious, but instead points to the "state of the art" and the declaration of their expert, Dr. Gregory. Defendants cannot properly bury supposed "substantial" invalidity arguments in the back of the 80 page declaration of one of its many experts.[36]

Putting aside their vagueness, the majority of Defendants' arguments seem to collapse to the same argument made with respect to the BRCA1 gene: that tools and techniques to identify and isolate genes were known and, thus, the BRCA2 gene must have been obvious. Once again, Defendants cannot support an obviousness claim simply by pointing out methods that a person of ordinary skill in the art could potentially use to reach the claimed invention. Such an argument is paramount to concluding that a novel engine is obvious because the ordinary skilled artisan would have access to a car shop and its tools. *See Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1351-52 (Fed. Cir. 2008) (affirming grant of preliminary injunction based on likelihood of prevailing on non-obviousness where prior art disclosed numerous possible techniques for delivering sustained release drug but possibilities were not finite or predictable); *In re Deuel,* 51 F.3d 1552, 1559 (Fed. Cir. 1995) ("The existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed DNAs.").

[36] While these arguments should not be given any weight, as explained in the Declaration of Dr. Kay, they all lack merit. Kay Decl. ¶¶118-26.

One of the references cited by Dr. Gregory, while not prior art, actually shows why the inventors' discovery of the BRCA2 gene was not obvious.[37] A short time after Myriad filed the patent application that led to the '857 patent, a research group led by Michael Stratton claimed to also have discovered the BRCA2 gene. Gregory Decl., Ex. Q. As it turned out, the BRCA2 structure referred to in Wooster (but not actually disclosed in Wooster) was incomplete at one end and contained a serious error at the other end. Kay Decl. ¶126; Tavtigan Decl. ¶6-20. At the N-terminus end, the protein was missing more than 280 amino acids. *Id*. At the C-terminus end, the proposed structure did not include the entire BRCA2 gene but instead included a large sequence of nucleotides that were ***totally unrelated and from a different chromosome.*** *Id*. These mistakes would not have been immediately apparent to those of ordinary skill in the art and could have led to serious problems with any attempted use of the "BRCA2" sequence. *Id*. If the inventors had not published the actual sequence of the BRCA2 structure, it is difficult to say when Wooster's mistake would have been discovered. *Id*. Moreover, even if these errors had eventually been discovered, it would have been no small task to identify the correct sequence of the BRCA2 gene starting from the work published by Wooster. *Id*. In short, even with access to all of the known tools and techniques for gene discovery, a group of highly skilled and financed scientists tried to identify and isolate the BRCA2 gene, and failed. *In re Cyclobenzaprine*, 676 F.3d at 1082-83 (finding failure of others to be strong evidence of nonobviousness).

[37] The Wooster article was published on December 21, 1995. Gregory Decl., Ex. Q. The application that led to the '857 patent was filed on December 18, 1995. *See* '857 patent. Accordingly, Wooster is not § 102(a) prior art because it was not described in a printed publication before the invention. Defendants also have not shown that Wooster is prior art under § 102(g) at least because (1) they have provided no corroborating evidence regarding what work the Stratton group did prior to December 18, 1995 and (2) the Stratton group was based in London (*see* Gregory Decl., Ex. Q) and, thus, any "invention" was not "made in this country," as required by 35 U.S.C. § 102(g)(2).

c. Given These Facts, the Discovery of the BRCA2 Gene Was Not Obvious Under *Kubin* or *KSR*.

For essentially the same reasons articulated for the '441 patent, *Kubin* is not relevant to the discovery of the BRCA2 gene. Because the BRCA2 protein and its amino acid sequence were not yet known, the existence of standard cloning or sequencing techniques does not suggest the gene's obviousness. *See In re Cyclobenzaprine*, 676 F.3d at 1070; *In re Bell*, 991 F.2d 781, 784-85 (Fed. Cir. 1993) (finding that human DNA sequences encoding IGF proteins were not obvious over references showing gene cloning method and complete amino acid sequences of IGFs).

Nor was the invention "obvious to try" because there was not a finite number of identified, predictable solutions. Here, a person of ordinary skill in the art would have essentially had to "vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result." *O'Farrell*, 853 F.2d at 903. That is precisely the situation in which the Federal Circuit has recognized that an "obvious to try" analysis is inappropriate. *Id.*; *see also In re Cyclobenzaprine*, 676 F.3d at 1072-73.

And, as explained above, even if the invention were "obvious to try," Defendants have not shown there was ***a reasonable expectation of success***. *See In re Cyclobenzaprine*, 676 F.3d at 1070 ("While it may have been obvious to experiment with the use of the same PK profile when contemplating an extended-release formulation, there is nothing to indicate that a skilled artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective."); *In re Brimonidine*, 643 F.3d at 1376 (rejecting Appellants' obvious to try argument where evidence supported that invention would not have been an "anticipated success).

4. Claims 2 and 4 of the ’155 patent Are Not Obvious in View of Miki, Friedman, or the ’282 Patent.

Claims 2 and 4 of the ’155 patent claim more effective methods of assessing an individual’s susceptibility to BRCA1-based hereditary cancer by using a “consensus sequence” for the BRCA1 gene. As explained in the ’441 patent, the consensus sequence (also identified in the claims as “SEQ. ID. NO: 1”) is the nucleic acid or protein sequence of the BRCA1 gene that occurs with the highest frequency in individuals who are not at risk of increased breast cancer. ’441 Patent at 3:29-59. By determining a consensus sequence, including the most common “neutral polymorphisms” found in individuals who are not at increased risk for cancer, the inventors enabled a method of testing that reduces the risk of misinterpreting a sequence variation (*i.e.*, a polymorphism or mutation) found in the normal population. ’441 patent at 2:5-33.

In the face of this inventive effort, Defendants nevertheless assert that two references cited on the face of the ’155 patent (Miki and Friedman) and Myriad’s own ’282 patent—none of which teach or in any way suggest a consensus sequence for the BRCA1 gene—render the claimed invention obvious. The Miki paper was published by Myriad and its collaborators in October 1994, and discloses the location and wild-type sequence of the BRCA1 gene. Miki also discloses five “predisposing mutations” in the BRCA1 gene and five “neutral polymorphisms.” Bowcock Decl., Ex. H at 170. Similarly, the Friedman paper, published in December 1994, discloses ten mutations in the BRCA1 gene linked to breast or ovarian cancer and nine “neutral polymorphisms.” Bowcock Decl., Ex. L at 403-03. The ’282 patent—one of Plaintiffs’ first patents related to the BRCA1 gene—discloses the wild-type sequence of the gene and, like Miki and Friedman, discloses several cancer-associated mutations and several neutral polymorphisms.

Defendants concede that none of Miki, Friedman, or the '282 patent disclose all of the polymorphisms recited in claims 2 and 4 of the '441 patent or a "consensus sequence" for the BRCA1 gene. Defs' Opp. at 66-68. Accordingly, claims 2 and 4 cannot be anticipated by Miki, Friedman, or the '282 patent.

Instead, Defendants incorrectly allege that these references teach a general method of identifying polymorphisms in the BRCA1 gene and, that in doing so, those references somehow render the identity of every possible polymorphism obvious. As explained earlier, such an argument is wrong as a matter of law. *See In re Deuel*, 51 F.3d at 1559 ("the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed DNAs"); *In re Bell*, 991 F.2d at 784-85.

Defendants' "general method" argument is also wrong on the facts because finding polymorphisms was not a predictable or straightforward task in the 1995 time frame. At that time, technologies for identifying polymorphisms were not well developed. Kay Decl. ¶135-36. Moreover, if a person of ordinary skill in the art discovered a polymorphism, they would have to take the additional step of determining the effect of the polymorphism (if any) with respect to the disease in question. Kay Decl. ¶136. Polymorphisms found in an intron region could cause changes in splicing or expression control, and one of ordinary skill in the art could only determine if such a polymorphism had a deleterious effect by observing the effect of the polymorphism in a familial population. *Id.* For polymorphisms found in an exon region, one would have to determine whether the polymorphism caused a change in the amino acid sequence. *Id*. If there was a change, they would have to go back to family data to see if there was any correlation between the altered amino acid and disease. *Id*.

Given these steps, there are many different directions that a person of ordinary skill in the art could take in trying to identify polymorphisms in the BRCA1 gene, and there is no evidence that a person of ordinary skill in the art would expect success in identifying and categorizing a particular polymorphism. Indeed, Miki acknowledges that "[t]he large size and fragmented nature of the [BRCA1] coding sequence will make exhaustive searches for new mutations challenging." Bowcock Decl., Ex. H at 172. Likewise, of its findings, the Friedman reference states that "[t]he mutations found, and not found, in these 20 families illustrate the complexities of screening for inherited BRCA1 mutations in families." Bowcock Decl., Ex. L at 403.

Finally, even if it were legally valid or factually correct, Defendants' "general method" rationale would not lead a person of ordinary skill in the art to the "consensus sequence"—*i.e.*, the BRCA1 sequence with seven ***specific*** neutral polymorphisms—claimed in the '441 patent. Nor would Defendants' rationale lead a person of ordinary skill in the art to perform genetic testing using this sequence in order to increase the reliability of the results. Defendants have fallen far short of meeting their burden to show that they are likely to prove the claims of the '155 patent are obvious.

5. Claim 5 of the '721 Patent Is Not Obvious in View of Miki, Friedman, or the '282 Patent.

Like the '441 patent, the '721 patent discloses a "consensus sequence" for the BRCA1 gene (also called the "omi[1] haplotype" or "SEQ ID. NO: 263") that represents the nucleic acid sequence of the BRCA1 gene that occurs with the highest frequency in individuals who are not at risk of increased breast cancer. '721 patent at 4:29-34, 22:21-53. The patent further provides that "the 'consensus' sequence of the BRCA (omi[1]) should be used as the only true standard for clinical diagnostic analysis in order to avoid misinterpreting polymorphisms as pathologic mutations." '721 patent at 25:48-51. Claim 5 recites a comparison between the nucleotide

sequence of a female individual to SEQ ID. NO: 263 to determine if the female has the omi[1] haplotype (and thus is not at an increased risk of cancer from BRCA1 mutation).

As with the '441 patent, Defendants assert that Miki, Friedman,[38] and the '282 patent each render claim 5 of the '721 patent obvious despite their concession that none of those references discloses the specific polymorphisms recited in claim 5 or a "consensus sequence" for the BRCA1 gene. Defs' Opp. at 66-68. Also like the '441 patent, Defendants argue solely that these references teach a general method of identifying polymorphisms in the BRCA1 gene and, thus, render every possible polymorphism obvious.

Claim 5 of the '721 patent is not obvious over these references for the same reasons articulated above for claims 2 and 4 of the '441 patent. Defendants' "general technique" arguments about these references are insufficient as a matter of law. *In re Bell*, 991 F.2d at 784-85. And, as explained above, Defendants' argument that these references would make it routine for a person of ordinary skill in the art to discover every polymorphism in the BRCA1 gene is also factually wrong. Kay Decl. ¶¶135-36. Moreover, even accepting Defendants' rationale would not lead a person of ordinary skill in the art to the "omi[1]" haplotype recited in claim 5 or the method of determining whether a female individual had that haplotype.

6. Objective Indicia Further Demonstrate that Defendants Have Not Raised a Substantial Question of Obviousness.

In analyzing a claim of obviousness, the Court must consider objective evidence of non-obviousness, also referred to as secondary considerations, which includes (i) whether there was a long-felt need for the claimed invention, (ii) failure of others to achieve the invention, (iii) industry praise and respect for the claimed invention; (iv) unexpected results from the claimed

[38] Miki and Friedman are both cited on the face of the '721 patent and were fully considered by the Patent Office. Miki is also cited in the body of the '721 patent. '721 patent at col. 2, ll. 18-21.

invention, (v) skepticism of others; and (vi) the commercial success of the claimed invention. *See, e.g., Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc.*, 711 F.3d 1348, 1368 (Fed. Cir. 2013).

The Federal Circuit has emphasized that the objective evidence may "often by the most probative and cogent evidence [of non-obviousness] in the record." *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009). This is because the objective evidence can "often serve as insurance against the insidious attraction of the siren hindsight when confronted with a difficult task of evaluating the prior art." *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983). It is an important "check against hindsight bias" because "knowing that the inventor succeeded in making the patented invention, a fact finder might develop a hunch that the claimed invention was obvious, and then construct a selective version of the facts that confirms the hunch. This is precisely why the Supreme Court explained that objective considerations might prevent a fact finder from falling into such a trap." *In re Cyclobenzaprine*, 676 F.3d at 1079.

The objective evidence here strongly supports a finding that Defendants have not demonstrated a substantial question that the claimed inventions—both the method and primer claims—are obvious.[39] There can be no doubt that there was a long felt need for the inventions, which, for the first time, provide a way to assess a patient's risk of developing hereditary breast or ovarian cancer by identifying mutations in the BRCA genes, thereby enabling the patient and her medical provider to develop a specific management plan for reducing that risk. Approximately 10% of breast cancers and 20-25% of ovarian cancers are inherited genetically.

[39] Defendants do not raise obviousness of the primer patents in their Opposition, but Defendants' experts raised some obviousness grounds in their declarations. Those arguments lack merit, Kay Decl., and the objective evidence discussed herein support the claims' nonobviousness.

Swisher Decl. ¶¶ 20-21. Prominent scientists at many companies and top research institutions worked for nearly 20 years to identify the gene that was linked to these hereditary cancers, essentially searching for a needle in a haystack with no real guidance. Mangum Decl., Ex. G.

After years of research, Myriad's scientists, using innovative approaches and techniques, were the first to sequence both the BRCA1 and BRCA2 genes, a task that was made more difficult by the complexity of the genes. Mangum Decl., Ex. K. Indeed, Dr. Skolnick, one of the inventors, explained that BRCA1 "is a very large gene 'that has no similarities to any other gene that we know of until the last segment that we found.'" Mangum Decl., Ex. L. Based on its extensive research, Myriad developed *BRACAnalysis*® genetic testing, which is covered by the patents-in-suit, to examine whether a patient has a mutation in one of the BRCA genes and characterize that mutation. Ford Decl. ¶ 1. Because BRCA mutations are responsible for the majority of hereditary breast and ovarian cancers, the results of the *BRACAnalysis*® testing enable a patient and her physician to develop specific plans aimed at reducing the risk of developing this hereditary cancer. *Id.* Even Defendants' experts recognize that genetic testing of this type is critical for clinical care to allow doctors and patients to plan strategies for preventive care and reduction of cancer. Swisher Decl. ¶¶ 22-24. Indeed, the *BRACAnalysis*® test has already benefitted over 1 million patients since its introduction on the market. Ford Decl. ¶ 1. Before the introduction of Myriad's patented test, there was no way for these patients to accurately evaluate their risk of developing these hereditary cancers. *BRACAnalysis*® filled the long-felt need for such a test.

Failure of others also supports the non-obviousness of the claimed inventions. Myriad was not the only company attempting to sequence the BRCA1 and BRCA2 genes. Indeed, many other companies and research institutions were also striving to determine the full sequence but

had failed to do so before Myriad. Mangum Decl., Ex. G. *See In re Cyclobenzaprine*, 676 F.3d at 1082 ("Long felt need is closely related to the failure of others. Evidence is particularly probative of obviousness when it demonstrates both that a demand existed for the patented invention, and that others tried but failed to satisfy that demand."); *Alco Standard Corp. v. Tenn. Valley Auth.*, 808 F.2d 1490, 1500 (Fed. Cir. 1986) (affirming finding of non-obviousness where the major manufacturers in the relevant industry had searched for more than a decade for a reliable solution and failed to develop one).

Even after Myriad sequenced the BRCA1 gene, other companies continued their attempts to sequence BRCA2 and continued to encounter problems in doing so. In December 1995, around the same time that Myriad succeeded in determining the full sequence of BRCA2, the Institute for Cancer Research ("ICR") published an article in *Nature* setting forth what it believed to be the cDNA and protein structures for BRCA2. But its structure was actually incorrect—instead of being the full sequence, it was incomplete at one end and contained a major error at the other. Tavtigian Decl. ¶¶ 5-9. Thus, despite its extensive research, ICR failed to determine the correct sequence for BRCA2, demonstrating the difficulty and unpredictability of the research in this field. The failure of others to develop the claimed inventions, despite significant efforts, is highly suggestive of non-obviousness. *See Cyclobenzaprine*, 676 F.3d at 1082.

The claimed inventions, which are embodied in Myriad's *BRACAnalysis*® tests, have also garnered significant recognition and praise in the field, further supporting their non-obviousness. *Crocs, Inc. v. U.S. Int'l Trade Comm'n*, 598 F.3d 1294 (Fed. Cir. 2010) (finding that "substantial industry praise for the claimed invention and the products covered by the claimed invention" supported non-obviousness). For example, Myriad's original sequencing

work was widely recognized and lauded, with the work itself being published in the journal *Science*, and both the press and other researchers applauding it as a "landmark discovery" and an "extraordinary advance for cancer research, opening the way for new and powerful ways to diagnose and treat breast cancer early." Mangum Decl., Ex. K; Ex. M ("[T]he public should know applying [the gene] will involve as much imagination and hard work as it took to find it."); Ex. C; Ex. L ("The discovery of BRCA1 is a major advance [that] will enable us to identify women, particularly younger women, who have an increased risk of developing breast cancer."); Ex. D. That praise and recognition continued with the groundbreaking *BRACAnalysis*® testing that Myriad developed based on its extensive work. Numerous doctors and medical societies have endorsed the tests as the first to provide patients with real, accurate information as to their risks of developing hereditary breast cancer. Mangum Decl., Ex. N and Ex. E.

Finally, the significant commercial success enjoyed by the patented inventions also supports their non-obviousness. "[A] presumption arises that the patented invention is commercially successful 'when a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent.'" *Ecolochem, Inc. v. Southern Cal. Edison Co.*, 227 F.3d 1361, 1376 (Fed. Cir. 2000). The cumulative revenue from the *BRACAnalysis*® tests, which are covered by the asserted claims, exceeds $2.5 billion. Kearl Decl. at 4.

F. Defendants Have Not Raised a Substantial Question that Claim 4 of the '155 Patent Lacks Written Description Support.

The written description requirement necessitates only that the patent applicant "convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991) (emphasis omitted). "It is not necessary that the application describe the claim limitations

exactly, but only so clearly that persons of ordinary skill in the art will recognize from the disclosure that [the inventors] invented processes including those limitations." *In re Wertheim*, 541 F.2d 257, 262 (CCPA 1976) (internal citation omitted).

Claim 4 of the '155 patent is directed to "[a] method of detecting an increased genetic susceptibility to breast and ovarian cancer in an individual resulting from the presence of a mutation in the coding sequence." The method provides for a comparison of a fragment of an individual's BRCA1 coding DNA with the disclosed consensus sequence of BRCA1 (SEQ. ID NO:1) to determine if there are any polymorphisms. The claim further recites seven polymorphisms that the patent refers to as reflecting the "normal" BRCA1 sequence and provides that, if a polymorphism other than one of those seven polymorphisms is detected in the test sequence, there is "the potential of increased genetic susceptibility to breast or ovarian cancer resulting from a BRCA1 mutation in the BRCA1 coding sequence." *See* '155 patent, tbl. IV.

Defendants incorrectly argue that the specification of the '155 patent does not provide written description support for claim 4 because it does not disclose any mutations that lead to increased susceptibility to breast cancer. Defs' Opp. at 74. Defendants' argument is misplaced because claim 4 does not require determining whether a particular polymorphism that is not found in the consensus sequence is actually disease-causing. Instead, the plain language of the claim simply provides that if the individual has a polymorphism other than one of the identified "normal" polymorphisms, then that person has ***the potential*** of increased genetic susceptibility to breast or ovarian cancer. In other words, claim 4 sets forth a method for identifying individuals who may have the potential for increased risk of breast cancer because they do not have the normal consensus sequence for BRCA1.

This plain meaning of the claim is supported by the specification. *See, e.g.*, '155 patent at col. 13, ll. 26-56; *id.* col. 16, l. 56 to col. 17, l. 10. It is further supported by the prosecution history because, in allowing claim 4, the Patent Examiner noted that "mutations identified will still have to be tested to determine whether they are themselves neutral or causative." Mangum Decl. Ex. O. Accordingly, the inventors did not need to provide examples of cancer-causing polymorphisms to convey that they were in possession of the invention, because the claim does not require knowledge of such polymorphisms. Defendants have thus not raised a substantial question as to whether claim 4 of the '155 patent is invalid for lack of written description.

G. Defendants Have Not Raised a Substantial Question that Claim 17 of the '282 Patent and Claim 30 of the '492 Patent Are Invalid As Indefinite.

1. Legal Standards for Indefiniteness.

A patent's specification "must conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor ... regards as the invention." 35 U.S.C. § 112(b). "A claim is indefinite only when it is 'not amenable to construction' or 'insolubly ambiguous.'" *Biosig Instruments, Inc. v. Nautilus, Inc.*, 715 F.3d 891, (Fed. Cir. 2013). "If the meaning of the claim is discernible, even though the task may be formidable and the conclusion may be one over which reasonable persons will disagree, we have held the claim sufficiently clear to avoid invalidity on indefiniteness grounds." *Exxon Research & Eng'g Co. v. United States*, 265 F.3d 1371, 1375 (Fed. Cir. 2001).

2. The Terms "BRCA1 gene" and "BRCA2 gene" Include cDNA Sequences.

Defendants' additional validity challenge to the asserted primer claims seeks to manufacture ambiguity where there is none. In arguing that the dependent primer claims are indefinite, Defendants erroneously apply a narrow meaning to the terms "BRCA1 gene" and "BRCA2 gene" in the independent primer claims that would encompass native DNA but not

cDNA, rather than a broader meaning of those terms that would encompass both native DNA and cDNA, and which is dictated by the claims' language and structure, the patents' specifications, and common usage of the term "gene" in the art. Under the correct construction, dependent claims 17 and 30 are understandable in context with, and further narrow, their respective independent claims. Because the dependent primer claims are amenable to construction, they are not indefinite.[40]

The independent primer claims use the terms "BRCA1 gene" and "BRCA2 gene," and the dependent primer claims provide that "said BRCA1[/2] gene has the nucleotide sequence set forth in SEQ ID NO:1." The dependent claims thus further limit the BRCA1 and BRCA2 genes of the independent claims to just cDNA, since SEQ ID NO:1 of both the '282 and '492 patents are limited to the cDNA of BRCA1 and BRCA2, respectively. The term "gene" as used in the broader independent primer claims should thus be viewed as including the cDNA sequence (SEQ ID NO:1) of the narrower dependent primer claims. *See Allergan, Inc. v. Barr Labs., Inc.*, 501 Fed App'x 965, 970 (Fed. Cir. 2013) (construing $-N(R^4)_2$ in independent claim as encompassing two non-identical R^4 substituents based on the entire patent, including dependent claim reciting two non-identical R^4 substituents); *AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1243 (Fed. Cir. 2003) ("Under the doctrine of claim differentiation, dependent claims are presumed to be of narrower scope than the independent claims from which they depend."); *see also Phillips v.*

[40] The district court in *Association for Molecular Pathology v. U.S. Patent & Trademark Office*, 702 F. Supp. 2d 181, 217 (S.D.N.Y. 2010), construed BRCA1 and BRCA2 from the '282 and '492 patents as follows: "'BRCA1' is therefore construed to refer to a human gene, normally integrated into chromosome 17, some alleles of which cause susceptibility to breast and ovarian cancer. Similarly, 'BRCA2' is construed to refer to a human gene, normally integrated into chromosome 13, some alleles of which cause susceptibility to breast and ovarian cancer." Neither claim 17 of the '282 patent, nor claim 30 of the '492 patent was at issue in the prior litigation. *Id.* at 212. The court did not construe the term "gene" or "BRCA1 gene" or "BRCA2 gene."

AWH Corp., 415 F.3d 1303, 1314 (Fed. Cir. 2005) ("Other claims of the patent in question, both asserted and unasserted, can also be valuable sources of enlightenment as to the meaning of a claim term.").

The specification not only confirms that interpretation, it expressly defines those terms as including cDNA as well and genomic or native DNA, among other things. The Federal Circuit has held that the specification is the "single best guide to the meaning of a disputed term." *Phillips*, 415 F.3d at 1315. Of even more importance here, that Federal Circuit has held that "the specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess. In such cases, the inventor's lexicography governs." *Id.* at 1316. This is just such a case.

The specifications of the '282 and '492 patents describe the terms "BRCA1 gene" and "BRCA2 gene"—as well as the terms "BRCA1[/2] locus"; "BRCA1[/2] nucleic acids" and "BRCA1[/2] polynucleotide"—as "refer[ring] to polynucleotides, all of which are in the BRCA1[/2] region, that are likely to be expressed in normal tissue, certain alleles of which predispose an individual to develop breast ovarian, or stomach cancers." '282 patent at 19:25-30; '492 patent at 18:12-17. The specifications further define, in reference to the terms "BRCA1 gene" and "BRCA2 gene," that "[t]he polynucleotide compositions of this invention ***include*** RNA, ***cDNA***, genomic DNA, synthetic forms, and mixed polymers . . . ." '282 patent at 19:51=53 (emphasis added); '492 patent at 18:36-38 (emphasis added). The specifications of the '282 and '492 patents further make clear that the terms "BRCA1 gene" and "BRCA2 gene," "when applied to a nucleic acid," as is the case in claims 17 and 30, "refer to a nucleic acid which ***encodes*** a BRCA1 [or BRCA2] polypeptide, fragment, homolog or variant." '282 patent at 19:25-50; '492 patent at 18:12-35 (emphasis added). The specifications offer ***SEQ ID NO:1***

(*i.e.*, the BRCA1 or BRCA2 cDNA sequences) as an example of a nucleic acid sequence that ***encodes*** a BRCA1/2 polypeptide. *See* '282 patent at col. 19, ll. 48-50.

Based on the specifications of the '282 and '492 patents, the terms "BRCA1 gene" and "BRCA2 gene," particularly in the context of nucleic acid sequences as set forth in the primer claims ("[a] pair of single-stranded DNA primers for determination of ***nucleic acid sequence of a BRCA1 gene***"), encompass cDNA in addition to native DNA, which contains both introns and exons. Both native DNA and cDNA ***encode*** a BRCA1 polypeptide. Accordingly, the terms "BRCA1 gene" and "BRCA2 gene" as used in the primer claims are amenable to construction and are not insolubly ambiguous. The independent primer claims encompass native DNA and cDNA, whereas the dependent primer claims are limited to cDNA.

Notably, Defendants effectively admitted this fact in another part of their opposition brief. In that part of the opposition, Defendants discuss other patents—the '441 and '857 patents—which have the same language (quoted above) in their specifications as the '282 and '492 patents, respectively. Defendants quote the same language as proof that "***[t]he patentee defined 'BRCA1 gene' to*** refer to 'polynucleotides' that ***include*** 'RNA, ***cDNA***, [or] genomic DNA' of BRCA1" in the '441 patent and then state that the same was true for BRCA2 based on the same language in the '857 patent. Defs' Opp. at 83, 85 (emphasis added). Given that admission, Defendants are foreclosed from arguing that the reference to the cDNA sequence in claims 17 and 30 is in any way inconsistent with the language of claims 16 and 29, let alone asserting that claims 17 and 30 are indefinite.

In any event, even though the patent's definition is controlling and renders extrinsic evidence irrelevant, construing the word "gene" to encompass both native DNA and cDNA is not only consistent with the claims' structure, it is also consistent with the usage of that term in the

art. Contrary to Defendants' contention, the term "gene" does not bear one absolute meaning to a person of ordinary skill in the art. Rather, it is a broad term with multiple potential meanings that are highly dependent on context. One the one hand, "gene" can be viewed as native DNA. In this regard, a "gene" can be considered in the context of chromosomes. A "gene," when thought of as native DNA, contains introns, exons, and regulatory sequences. *See* Roa Decl. (Dkt.#7), ¶13. On the other hand, "gene" can be viewed more broadly as referring to polynucleotides, including native DNA or cDNA. Persons of ordinary skill in the art sometimes use the term "gene" to refer to anything that encodes the corresponding protein, including either native DNA having both exons and introns, or just the coding portions of such native DNA, *i.e.*, cDNA. Kay Decl. ¶ 65. Context is therefore key in understanding how the term "gene" is being used. In any event, these ordinary meanings provide "an objective baseline from which to begin claim interpretation." *Phillips,* 415 F.3d at 1313.

Further, Defendants' own expert demonstrates the amenability of claims 17 and 30 to construction. For example, Dr. Gregory explained, "For the purpose of comparing claim 17 with prior art, I assume claim 17 means that the corresponding cDNA of the BRCA1 gene 'has the nucleotide sequence set forth in SEQ ID NO:1.'" Gregory Decl., ¶ 89; *see also id.* ¶ 241. Dr. Gregory, however, misinterprets the scope of the terms "BRCA1 gene" and "BRCA2 gene" by requiring the corresponding DNA to exist in "normal tissue." He then excludes cDNA from the definitions of "BRCA1 gene" and "BRCA2 gene" because it does not exist in normal tissue, but instead is derived by reverse transcription of mRNA. But Dr. Gregory's proposed construction of these terms ignores the rest of the specification which, as described above, explains that in referring to nucleic acid sequences, BRCA1 gene and BRCA2 gene refer to sequences that encode the BRCA1 or BRCA2 polypeptide, and that the specifications only state that the

BRCA1/2 genes are "likely" to exist in native tissue. *See* '282 patent at col. 19, ll. 26-29. He also ignores the use of the terms in the context of and the interplay between the dependent and independent primer claims. In other words, in those contexts, the terms refer to cDNA, just as the specification explains the polynucleotides are supposed to encompass. Accordingly, "BRCA1 gene" and "BRCA2 gene" are properly construed to include both native DNA and cDNA. Claims 17 and 30—which require SEQ ID NO:1, or cDNA—thus properly narrow claims 16 and 29 which more broadly refer to "BRCA1 gene" and "BRCA2 gene." The patents broadly describe those terms as encompassing any sequence encoding a BRCA1 or BRCA2 protein (including SEQ ID NO:1 or cDNA), and they should be construed in conformity.

II. THE FACTORS OF IRREPARABLE HARM, BALANCE OF THE HARDSHIPS AND PUBLIC INTEREST FAVOR ENTRY OF AN INJUNCTION.

A. Myriad Will Suffer Immediate and Irreparable Injury If Injunctive Relief Is Not Granted.

In its Motion, Myriad sets forth four specific categories of immediate and irreparable harm that it will suffer if Defendants are not enjoined from their infringing activity, including irreversible price erosion, loss of market share, reputational injury, and loss of the benefit of its remaining limited term of patent exclusivity. Plfs' Ambry Mot. at 30-41; Plfs' GBG Mot. at 26-36. Myriad further set forth extensive authority from the Federal Circuit and other federal courts recognizing that these forms of damages constitute irreparable harm that warrant the imposition of injunctive relief. *See id.*[41]

[41] Citing *Robert Bosch LLC v. Pylon Mfg. Corp*., 659 F.3d 1142, 1152-54 (Fed. Cir. 2011) (injunction should have been granted due to "evidence of loss of market share and access to potential customers," and the patentee suffered "irreversible price erosion, loss of market share, loss of customers, and loss of access to potential customers."); *Douglas Dynamics, LLC v. Buyers Products Company*, Nos. 2011–1291, 2012–1046, 2012–1057, 2012–1087, 2012–1088, 2013 WL 2158423 at *5-6 (Fed. Cir. May 21, 2013) ("[i]rreparable injury encompasses different types of losses that are often difficult to quantify, including lost sales and erosion in reputation and brand distinction").

Defendants do not attempt to distinguish or overcome the authority cited by Myriad. Indeed, their opposition is notably devoid of authority or analysis. Instead, they rely upon generalized assertions of an accountant expert regarding Myriad's alleged ability to maintain or restore its prices that ignore fundamental economic realities and established case law. Defendants have not countered Myriad's specific, particularized showing of harm, and, more importantly, have not (and cannot) overcome the fact that the harm threatened to Myriad is exactly the type that injunctions are intended to address.

1. The Price Erosion that Myriad Will Suffer if Defendants Are Allowed to Proceed Is the Very Type of Irreparable Harm that Justifies Entry of an Injunction.

Myriad demonstrated that a patentee is entitled to practice its right of exclusion by pricing its patented products accordingly, and an infringer may substantially and irreversibly damage that right by offering infringing products at deeply discounted prices such as those offered by Defendants. Plfs' Ambry Mot. at 31; Plfs' GBG Mot. at 27; *see* Defs' Opp. at 15, ¶ 46 (acknowledging that Ambry is offering its competing test at $2,200, and Gene by Gene at $995, compared to Myriad's at $4,040). It further demonstrated that, if Defendants are allowed to enter and remain in the market, Myriad will lose significant amounts of revenue because Myriad will be pressured to lower its prices, will be forced to do so in some instances, and market prices will decline. For this reason, Myriad will further lose the benefit of its pricing policy and efforts at building the market. Plfs' Ambry Mot. at 32; Plfs' GBG Mot. at 28. Myriad set forth extensive authority, which Defendants do not even address, which holds unequivocally that such circumstances constitute irreparable harm. *Sanofi–Synthelabo, Inc. v. Apotex, Inc*., 470 F.3d 1368, 1382-83 (Fed. Cir. 2006) (affirming grant of an injunction where the patentee employed a complex pricing scheme that was "directly affected by the presence of the generic product in the market" as the patentee was "forced to offer discounted rates and price

concessions to third-party payors, such as health maintenance organizations, in order to keep Plavix® on a favorable pricing tier, which governs what consumers pay for that drug"); *Purdue Pharma L.P. v. Boehringer Ingelheim GmbH*, 237 F.3d 1359, 1368 (Fed. Cir. 2001) (likelihood of price erosion and loss of market position are evidence of irreparable harm).

In opposition, Defendants rely upon two principle assertions made by Mr. Hampton: (1) Myriad has not yet dropped its prices and, because of its solid financial footing, could maintain its pricing even in the face of competition (Defs' Opp. at 88-89); and (2) price erosion is in any event measurable. *Id*. at 90. Both assertions fail upon examination. First, Defendants make much of the fact that Myriad did not offer evidence of specific pricing changes in response to Defendants' "entry into the market some two months ago." Defs' Opp. at 88-89; Declaration of Scott Hampton, C.P.A. (Dkt. #58) ("Hampton Decl.") at 10, ¶¶ 26-29; 43. At the outset, Defendants' claim is inconsistent with their assertion that Ambry only "offered to sell" and Gene by Gene has "announced its intentions to sell" testing services. Defs' Opp. at 82. More importantly, Defendants fail to address the fact that Myriad brought this lawsuit, and sought a preliminary injunction, ***precisely to avoid*** an immediate response in pricing that would result in price erosion. Defendants correctly state that Myriad has maintained its pricing in reliance upon its patent exclusivity. *Id*. at 88. Indeed, Myriad's ability to maintain the benefit of its pricing throughout this period is all the more critical given the pending expiration of Myriad's patents, which constitutes another specific form of irreparable harm that Defendants do not address. *Pfizer, Inc. v. Teva Pharmaceuticals, USA, Inc*., 429 F.3d 1364, 1380 (Fed. Cir. 2005) (the district court properly considered the fact that "[defendant's] sales of its generic product would cause substantial harm to [patentee] and loss of the statutory right to exclude [defendant] for the remaining life of the '450 patent, which expires in August 2007").

Nor is there any justification for Defendants' argument that Myriad could simply maintain its current pricing, even in the face of direct competition by Defendants and potentially others. Hampton Decl., ¶¶ 27-29. Were Myriad to do so, it indisputably would stand to lose significant sales, which are exceedingly difficult to even estimate at this juncture—the very definition of irreparable harm. Kearl Decl. at 8-9. The fact that Myriad's pricing is primarily established through contracts with third-party payors does not ameliorate this harm. Defs' Opp. at 89; Hampton Decl., ¶ 28. In his Declaration, Mr. Ford explained that "some third-party payors have already begun to exert pressure on Myriad to lower its prices in response to Ambry's discounted tests. In some instances, Myriad may be forced to do so in order to compete with Ambry." Ford Decl., ¶ 16. The fact that some of Myriad's third-party contracts may not be subject to change until later this year does not obviate the harm to Myriad that will occur absent an injunction once renegotiations begin.[42]

Defendants' alternative argument that Myriad would not be damaged absent entry of an injunction because it could simply reinstitute its pricing at the conclusion of the lawsuit (Defs' Opp. at 89; Hampton Decl., ¶¶ 27) is also devoid of economic reality. Mr. Hampton merely asserts that Myriad could accomplish such a feat. In reality, Myriad cannot simply "unring the bell" and return the market to the pre-infringement position. There would be significant customer resistance, and it is highly unlikely that Myriad could ever restore the pre-infringement status quo, particularly in its limited remaining period of patent exclusivity. Dr. Kearl cites to the extensive economic literature that recognizes that even cartels and monopolists meet

[42] Nor is the foregoing altered by Mr. Hampton's suggestion that Myriad could simply offer its new myRisk™ multi-gene panel at the current price of its BRACAnalysis® test ($4,040). Hampton Decl., ¶ 26. Again, this is the very definition of irreparable harm. Patent exclusivity should give Myriad the ability to recover appropriate compensation for its exclusive offering. Forcing Myriad to essentially "give away" other tests in conjunction with its exclusive tests does not make Myriad whole.

significant customer resistance when they attempt to impose prices that the customers find unjustified. In fact, after signaling that a lower price is possible, firms generally face tremendous buyer resistance to higher prices. Kearl Decl. at 10-11.

The Federal Circuit recently rejected an analogous argument in *Aria Diagnostics, Inc.* There, the district court found that "erosion to [patentee's] price and its loss of market share were not irreparable." 2013 WL 4034379 at * 7. The district court based its finding on the argument that, if patentee were proven correct, it could "recover the market and receive damages to compensate for the infringement." *Id.* In finding this conclusion to be in error, the Federal Circuit held:

> While the *facts* may show that damages would be reparable, this *assumption* is not sufficient. In the face of that kind of universal assumption, patents would lose their character as an exclusive right as articulated by the Constitution and become at best a judicially imposed and monitored compulsory license.

Id. (emphasis original). *See also Polymer Tech. Inc. v. Bridwell*, 103 F.3d 970, 975-76 (Fed. Cir. 1996) ("Competitors change the marketplace. Years after infringement has begun, it may be impossible to restore a patentee's (or an exclusive licensee's) exclusive position by an award of damages and a permanent injunction. Customers may have established relationships with infringers. The market is rarely the same when a market of multiple sellers is suddenly converted to one with a single seller by legal fiat. Requiring purchasers to pay higher prices after years of paying lower prices to infringers is not a reliable business option.").

Finally, Dr. Hampton's assertion that "it is highly doubtful" that the licensor plaintiffs will suffer irreparable injury (Hampton Decl., ¶ 39) is contradicted by Dr. David W. Pershing's testimony that, over the past two decades, Myriad has paid over $40,000,000 in royalties to the University of Utah Research Foundation pursuant to some of the patents at issue here.

Declaration of David W. Pershing ("Pershing Decl."), ¶ 4. These payments have increased over the years, and provide important financial support for ongoing research efforts. *Id.*, ¶ 5. See Declaration of Thomas N. Parks ("Parks Decl."), ¶¶ 3-7) ("Technology commercialization is a vital part of the mission of any research university . . . The licensing of new discoveries to companies enables the University of Utah to fulfill its mission to benefit society through the creation and commercialization of new products from its research discoveries."). A decline in Myriad's revenue due to infringing sales will certainly impact payments to the University and the other licensors, and thus impact such ongoing efforts.

2. <u>The Harm Myriad Will Suffer in the Form of Price Erosion Cannot Be Readily Compensated.</u>

Defendants are also incorrect in their contention that any price erosion damages suffered by Myriad would be measurable and compensable. Defs' Opp. at 90; Hampton Decl., ¶¶ 28, 31-33, 40-43. Critically, Defendants do not address the extensive authority cited by Myriad, which holds that the question is not whether damages would be "impossible" to quantify (Defs' Opp. at 90); rather, it is whether the infringer's entry into the market will result in damages that are "difficult to quantify" or "rarely reversible." *Douglas Dynamics, LLC,* 2013 WL 2158423 at *5-6 ("[i]rreparable injury encompasses different types of losses that are often difficult to quantify, including lost sales and erosion in reputation and brand distinction"); *Abbott Labs.,* 544 F.3d at 1361-62 (Fed. Cir. 2008) (affirming entry of a preliminary injunction because patentee "could not be made whole if it prevails in this litigation, for the added erosion of markets, customers and prices, is rarely reversible").[43]

[43] *Eli Lilly & Co. v. Am. Cyanamid Co.*, 82 F.3d 1568 (Fed. Cir. 1996), cited by Defendants, is not to the contrary. Defs' Opp. at 90. In that case, the district court specifically found that "[i]n light of the structure of the [relevant] market," "calculating lost profits would be a relatively simple task." *Id*. at 1578. Defendants have made no such showing here.

Furthermore, Defendants only assert the conclusion that the damage to Myriad would be compensable. For example, Mr. Hampton states that "the Court can remedy Myriad through a monetary award. The difference between Myriad's original price and the actual price it experiences can be quantified and remedied." Hampton Decl., ¶ 31. But this is a sleight of hand by Mr. Hampton. Price erosion damages would be the difference between the prices multiplied by the unit sales Myriad would have made if the price had not declined. As Dr. Kearl shows, both terms in the price erosion formula in this case will be unknown. For example, Mr. Hampton simply assumes that one price exists now and that absent the injunction Myriad would simply set a lower price. This is not true. Myriad's prices differ by type of test, customer, and time period. Kearl Decl. at 11-14. To determine what the numerous prices would have been in the "but for" world would be very difficult. Moreover, the customers who Myriad would have charged these "but for" prices similarly are unknown. *Id*., at 14, 16-17. Once prices decline, all new customers will pay the lower price. How can one possibly determine which of these customers who bought at the lower price would have paid the higher price if the injunction had issued?

Despite Mr. Hampton's claims, the likely scenario is that, if Ambry and Gene by Gene are allowed to proceed, some customers that otherwise would have purchased Myriad's test at a higher price will purchase a test from Defendants, and some customers that would not have purchased Myriad's test nonetheless will purchase Defendants' tests. As Dr. Kearl explains (Kearl Decl. at 13-16), it will be extremely difficult to distinguish between those two groups, and Mr. Hampton has offered no analysis to the contrary. These factors, taken as a whole, compel the conclusion that the price erosion damage Myriad would suffer from Defendants' sales would be irreparable. *See, e.g., Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d at 1381 ("We are not persuaded by Apotex's assertion that Sanofi contracted away its right to prove irreparable harm

by entering into [an agreement] which includes a provision that capped damages for infringement by Apotex."). In other words, the mere existence of a ***potential*** basis for awarding damages does not negate a finding of irreparable harm.

Similarly, by referring to the potential that other competitors will enter the market (Hampton Decl., ¶¶ 27, 30), Mr. Hampton only underscores the difficulty in estimating damages to Myriad. *See* Kearl Decl. at 15-16. In the damages phase of an infringement suit Myriad will be obligated to establish how much price erosion is "caused" by the particular plaintiff in each case. There is no joint and several damages for infringement as Mr. Hampton posits. [44]

3. Myriad Will Lose Market Share If Defendants Are Allowed to Proceed, Regardless of Any Alleged Market Expansion.

As Myriad explained, it is certain to lose market share if Defendants are allowed to enter, whether it lowers its prices or not. This is because, given Defendants' significantly discounted prices, some third-party payors will insist that patients choose Ambry or Gene by Gene over Myriad solely because of cost. Plfs' Ambry Mot. at 35; Plfs' GBG Mot. at 33. This loss of market share provides ample basis for finding irreparable harm. *Presidio Components, Inc. v. American Technical Ceramics Corp*., 702 F.3d 1351, 1363 (Fed. Cir. 2012) ("[d]irect competition in the same market is certainly one factor suggesting strongly the potential for irreparable harm without enforcement of the right to exclude"); *TiVo Inc. v. EchoStar Comm'ns*

[44] Similarly, the existence of other potential competitors does not equate to a finding that Myriad "inconsistently" enforces its patents, or that other elements of Myriad's irreparable harm claim are lacking. Defs' Opp.at 92; Hampton Decl., ¶¶ 27, 30 & 47. Federal Circuit precedent uniformly holds that "a patentee need not sue all infringers at once. Picking off one infringer at a time is not inconsistent with being irreparably harmed." *Robert Bosch, LLC*, 659 F.3d at 1151 (citing *Pfizer, Inc*., 429 F.3d at 1381). The *Robert Bosch* court went on to note that "[w]ere we to conclude otherwise, we would effectively establish a presumption against irreparable harm whenever the market contains a plurality of players." *Id. See also Aria Diagnostics, Inc*., 2013 WL 4034379 at * 7 ("the 'fact that other infringers may be in the marketplace does not negate irreparable harm'") (citing *Pfizer, Inc*., at 1381).

Corp., 446 F. Supp. 2d 664, 669-70 (E.D. Tex. 2006), *rev'd in part on other grounds*, 516 F.3d 1290 (Fed. Cir. 2008) (finding irreparable harm where defendant was a direct competitor and stating that "[t]he impact of Defendants' continued infringement is shaping the market to Plaintiff's disadvantage and results in longterm customer loss. This is particularly key where, as is the case here, Plaintiff's primary focus is on growing a customer base specifically around the product with which Defendants' infringing product competes").

Defendants argue in opposition that they will increase the size of the market by offering discounted pricing, implying that Myriad will not actually lose market share, and that any such loss would in any event be calculable. Defs' Opp. at 90-91; Hampton Decl., ¶¶ 44-45. First, as set forth above, there is no basis for Defendants' implication that ***all*** of the customers for their products are individuals who would not have purchased Myriad's test. Accordingly, there will be at least some patients who buy Defendants' tests, but otherwise would have been Myriad customers. While the size of the market will expand, identifying those "Myriad customers" will be extremely difficult. Indeed, Mr. Hampton implicitly acknowledges this fact by stating that "new entrants, including Ambry and Gene by Gene, ***will not always compete directly*** with Myriad. . . ." Hampton Decl., ¶ 45 (emphasis added). It is those instances when Defendants ***do*** compete directly with Myriad that are at issue here, and the fallacy of Defendants' argument is the supposition that this customer segment can be identified. Kearl Decl. at 9.

Defendants' remaining arguments regarding their alleged ability to provide "meaningful second opinion testing" and multi-gene panel and large rearrangement testing (Defs' Opp. at 90; Hampton Decl., ¶46) are merely an extension of their "market expansion" argument, and fail for

the same reasons.[45] Even if Defendants obtain some customers that otherwise would not be in the market by virtue of these alleged "benefits," that does not change the fact that determining the identity of those customers to enable Myriad to advance a damages theory based upon loss of market share would be very difficult, a harm that can and should be remedied by issuance of a preliminary injunction.

4. Loss of Patent Exclusivity and Related Investment and Reputational Harm Are Independent Elements of Irreparable Harm.

Defendants' Opposition is virtually silent on Myriad's showing that loss of the ability to benefit from its limited remaining term of patent exclusivity qualifies as irreparable harm. *Pfizer, Inc.*, 429 F.3d at 1380; *see also Hybritech*, 849 F.2d at 1456 (noting the fact that "by the time the litigation is finished, it is entirely possible that the value of the patent will be gone and that technology might well bypass it" and the fact that, absent injunction, "other potential infringers will be encouraged to infringe"); *see* Myriad's Ambry Mot. at 39; Myriad's GBG Mot. at 35.

Nor have Defendants countered Myriad's showing that in the absence of an injunction it will lose the benefit of its significant expenditure in developing the market, as well as its corporate strategy for its remaining years of patent exclusivity, including the ability to bring its myRisk Hereditary Cancer™ test to market during the remaining patent term. *Id*. at 39-40; *id*. at 35-36. Myriad supported its claim of a $500 million investment in developing the market for genetic predisposition cancer testing with the Declaration of Alexander Ford, the Chief

[45] Additionally, for the reasons set forth in Myriad's Objections to Evidence, filed concurrently herewith, testimony regarding "second opinion testing" is exactly the type of policy-based argument that the Federal Circuit has held properly committed to legislative determination. Furthermore, as set forth in Myriad's public interest discussion (Section II(C), *infra*), Defendants' assertions are factually inaccurate. In any event, Myriad is on record that it will not enforce its patents against companies providing second opinion testing to patients who have already received a test from Myriad. Ford 2nd Decl., ¶ 6.

Commercial Officer of Myriad Genetic Laboratories, Inc. Dkt. # 6 (Case No. 2:13-cv-00640), ¶ 4; Dkt. # 7 (Case No. 2:13-00643), ¶ 4. As Mr. Ford explained, BRAC*Analysis*® testing has been on the market since 1996, and, as the developer and only provider of such tests, Myriad created and developed the market through substantial capital investments in time and money. Myriad's efforts included conducting extensive clinical studies in support of medical industry guidelines regarding hereditary cancer predisposition testing, developing a market of insurance reimbursement for such testing, and promoting physician and patient education surrounding the importance of such testing. *Id*., ¶ 3; *id*., ¶ 4. To do so, Myriad had to convince both private and public health insurers that the type of testing performed by BRAC*Analysis*® is not only in the public health interest, but saves the healthcare system money by preventing diseases. *See id*.

While Defendants' brief is silent as to these forms of irreparable harm, Mr. Hampton states that the amount of Myriad's investment "appears unreasonable," and argues that Myriad already has obtained the benefit of its investment, or has accounted for these losses. Hampton Decl., ¶¶ 51-54. Mr. Hampton's purported doubts regarding the amount of Myriad's expenditures is insufficient to overcome Myriad's specific showing. Nor does he even attempt to address Myriad's showing regarding its significant efforts in creating the market of insurance reimbursement for such testing.[46] And, neither the fact that Myriad has enjoyed financial success, nor the fact that it has appropriately advised its investors that it has modified its revenue projections in light of Defendants' entrance into the market, have any bearing upon the issue of

[46] The Declaration of David H. Ledbetter, Ph.D. (Dkt. #'s 60 and 45), relied upon by Mr. Hampton, does not further Defendants' argument. Dr. Ledbetter criticizes the quality of Myriad's tests, but does not dispute the amount of its investment. *Id*., ¶¶ 20, 26. And, he challenges Myriad's statements regarding its efforts in creating the market, but only to the extent that the need for such testing "was already a national concern and priority." *Id*., ¶¶ 24, 29. Myriad does not claim that it created the ***need*** for genetic predisposition testing for certain hereditary cancers, but that it created the system that allowed such testing to take place, primarily with respect to the development of standards and reimbursement.

irreparable harm. Myriad is entitled to the financial benefit of its entire statutory term of patent exclusivity, absent any arbitrary cut-off that Mr. Hampton would impose. Defendants have not overcome Myriad's showing that allowing them to "piggyback" off of Myriad's seventeen years of investment in time, effort, and money constitutes irreparable harm.

Finally, Myriad explained that allowing Defendants to enter the market will result in non-compensable damage to Myriad's reputation. This is because Myriad was the only provider of genetic predisposition testing for breast and ovarian cancer until a few months ago, and thus providers and patients naturally associate the test with Myriad. Plfs' Ambry Mot. at 38; Plfs' GBG Mot. at 33. While Defendants dispute the quality and accuracy of the BRACAnalysis® test, allegations which are flawed for the reasons set forth in the discussion regarding the public interest factor, *infra*, the fact remains that dilution of Myriad's reputation by Defendants' tests is a significant risk giving rise to a finding of irreparable harm.[47] *Douglas Dynamics, LLC*, 2013 WL 2158423 at * 5-6 (patentee could lose its "distinctiveness and market lure" and reputation as an "innovator" if defendant were to enter the market). Kearl Decl. at 18-19.

B. The Balance of Hardships Favors Myriad's Patent Exclusivity Interest Over Defendants' "Headstart" Interest.

In its Motion, Myriad explained that, even though there is no requirement that the Court expressly find that the balance of hardships tips in favor of the patentee to award an injunction (*Hybritech*, 849 F.2d at 1457), that balance nonetheless weighs heavily in Myriad's favor.

[47] Defendants' assertion that genetic counselors and insurance providers would not be confused by the introduction of competing tests (Defs' Opp. at 91) does not adequately address Myriad's argument. Myriad explained that third-party payors typically select the provider based on cost, rather than the consumer or her health care provider, which means that consumers are likely to associate flawed test results with Myriad. Plfs' Ambry Mot. at 38; Plfs' GBG Mot. at 33. Nor do Defendants address the fact that Myriad has had no time or opportunity to distinguish its BRAC*Analysis*® test and associated testing quality from competitors as it would if competitors were barred from entry until the patents' expiration, such as via the marketing strategy it had begun to formulate. *Id*. at 38; *id*. at 33.

Myriad has made BRCA1 and BRCA2 testing a significant part of its business model and relied heavily upon its patent exclusivity. Defendants, on the other hand, are new entrants to the market (assuming that they have entered the market at all, upon which point Defendants have made conflicting assertions). Defs' Opp. at 82.

In response, Defendants interject a theory of hardship based upon their alleged investment in developing a competing product, and related "headstart" in the marketplace. Defendants argue they will "lose their valuable headstart" and "distinct advantage in terms of initial market penetration and the ability to eventually obtain a strong market position." Defs' Opp. at 94; *see id*. Hampton Decl., ¶¶ 58-61.

Defendants' balance of the hardships argument improperly credits the potential loss of Defendants' investment and alleged headstart over Myriad's right under the United States patent laws to capitalize on its remaining period of exclusivity. In premising their business strategy upon the assumption that Myriad's patent claims pertaining to synthetic DNA and related methods would be held invalid, Defendants chose to take a gamble. Defendant Ambry in particular claims to have invested $46.7 million "in anticipation of the invalidation of Myriad's patents." Defs' Opp. at 94. Thus, Ambry did not even wait for the Supreme Court's opinion, but instead chose to bet heavily on its desired outcome. Now, faced with a decision that pertains only to a small subset of Myriad's patent claims, Ambry is seeking to have this Court protect it from the consequences of its gamble. This is both improper and premature. It remains to be seen whether Ambry's gamble will pay off, and Ambry cannot prematurely "collect" on its bet by avoiding an injunction.

Indeed, such a result would be contrary to established authority on this factor. An analogous argument was rejected in *Ortho Pharmaceutical Corp. v.*, 15 U.S.P.Q.2d 18563 (E.D.

Pa. 1990). There, the court found that the balance of the hardships favored the patentee where "the hardship Ortho will suffer by virtue of costs it has incurred in developing and preparing to market an infringing product are ***attributable solely to Ortho's calculated decision to bring [its product] to market prematurely . . .*** . One who elects to build a business on a product found to infringe cannot be heard to complain if an injunction against continuing infringement destroys the business so elected." *Id*. at 1863 (emphasis added). Furthermore, defendant's "sole allegation of damage" in that case was, like Ambry's, "a return on an investment of about 50 million dollars" which did not outweigh patentee's "lost sales and market share." *Id. See Critikon v. Becton Dickinson Vascular Access Inc.*, 28 U.S.P.Q.2d 1362, 1371 (D.Del. 1993) (finding that balance of hardships favored preliminary injunction where "Becton Dickinson is still in the early stages of marketing its safety catheter, whereas Critikon's product has been on the market for over a year. The hardship facing Becton Dickinson in delaying its entry into the market three to six months is not as severe as that faced by Critikon by not being able to enforce its apparently valid patent, and the potential harm that will result to its reputation and goodwill as an innovator in the safety catheter market.");[48] *American Parking Meter Adv., Inc. v. Visual Media, Inc*., 693 F.Supp. 1253, 1255 (D.Mass. 1987) (Noting that, if the patent is valid, "there would be irreparable injury if the defendants were permitted to continue with infringement during the pendency of this action. Patents are entitled to receive special protection. Delay may well become the equivalent of an involuntary license by the patent holder.").

[48] In *Glaxo Group Ltd. v. Apotex, Inc*., 64 Fed.Appx. 751 (Fed. Cir. 2003), the court rejected a similar argument from an infringer that it had put a "huge amount of investment . . . into preparing to bring" its product to market, and "stands to lose millions of dollars a month as a result of the delay in the market entry." *Id*. at 756. It held that an injunction was warranted where "Glaxo would lose the value of its patent" while "Apotex would only lose the ability to go on to the market and begin earning profits earlier." *Id*. The court relied in part upon the fact that Apotex was secured by the issuance of a bond. *Id*.

Defendants' remaining claims of "hardship" similarly fail. They claim that Myriad already has been "made whole," by virtue of the years it has benefitted from monopoly pricing (Defs' Opp. at 93), but cite no authority in support of the assertion that an infringer may impose an arbitrary cutoff on a patentee's right to capitalize on its period of patent exclusivity. In fact, the controlling authority cited by Myriad in its opening brief, holds the opposite. Plfs' Ambry Mot. at 31, 39; Plfs' GBG Mot. at 27, 35. Nor can Ambry resort to authority considering the fact that an injunction may put the defendant out of business. Ambry has made no such factual showing. While claiming that an injunction would result in the loss of its $46.7 million bet on BRCA1 and BRCA2 testing, Ambry never states that its business is premised upon such testing. To the contrary, it states that "Ambry is by no means a newcomer to the hereditary cancer testing market. Since 2003 Ambry has been building what is now the most comprehensive hereditary cancer testing menu available." Defs' Opp. at 95. For this reason, Ambry has not and cannot credibly assert that an injunction would "put it out of business."

Moreover, rather than supporting Ambry's position, if Ambry were in fact in a precarious financial position as a result of its $46.7 million gamble, that fact would only further support Myriad's irreparable harm. *See Robert Bosch, LLC*, 659 F.3d at 1152 (district court erred in concluding that patentee failed to demonstrate irreparable harm where, among other things, it had introduced evidence regarding the defendant's "inability to satisfy a judgment"). Furthermore, as discussed above, any financial harm associated with Ambry's investment in the BRCA market cannot outweigh the harm to Myriad, as a patent owner. *Abbott Labs. v. Sandoz, Inc.*, 500 F.Supp.2d 807, 845 (N.D. Ill. 2007) (" it should go without saying that one who infringes upon a patent cannot be heard to complain about the financial consequences of either ending its infringing conduct or being restored to its pre-infringement position").

C. The Public Interest Favors an Injunction.

The focus of the public interest analysis is whether "there exists some critical public interest that would be injured by the grant of preliminary relief." *Hybritech*, 849 F.2d at 1458. No such interest exists here. To the contrary, "the public has a greater interest in acquiring new technology through the protections provided by the Patent Act than it has in buying 'cheaper knock-offs'." *Douglas Dynamics*, 2013 WL 2158423 at *7. Myriad demonstrated that the public interest was best served by issuance of a preliminary injunction, as Myriad is fully serving the market need with its test of proven efficacy. Defendants' assertions to the contrary fail upon examination.

1. Myriad's BRACAnalysis® Test Has Fully Met the Need for Hereditary Predisposition Testing for Breast and Ovarian Cancer Since 1996, and Exhibits Unparalled Reliability.

As Myriad explained, the Federal Circuit has recognized that "[t]he statutory period of [patent] exclusivity reflects the congressional balance of interests, and warrants weight in considering the public interest." *Abbott Labs*, 544 F.3d at 1362. For this reason, the public interest in recognizing and incentivizing inventive work such as that performed by Myriad ***by itself*** may outweigh any purported "interest" in obtaining inexpensive infringing products. Plfs' Ambry Mot. at 42; Plfs' GBG Mot. at 37-38.

Myriad went even further, however, and demonstrated that precluding Defendants from selling unproven and less accurate tests is in the public interest because Myriad already provides testing of very high quality, accuracy and affordability, which means that the public interest is currently being well served by Myriad's testing. In support, Myriad cited its years in the market to perfect its testing processes that have resulted in a near-perfect accuracy rate, as well as its exclusive access to its proprietary and extensive database of known genetic variants when

making a comparison with a patient test sample which allows it to report definitive findings to over 97% of its patients. Ford Decl., ¶¶ 5-7.

In contrast, Defendants' tests have not been subjected to the extensive time on the market, period of development, and rigorous assessment and thus they cannot offer the same level of reliability. Geier Decl., ¶ 29. In particular, Ambry's failure rate may be as high as 4%, and the VUS rate of both Defendants is likely higher than their reported rates. *Id*.; Eggington Decl., ¶ 9; Plfs' Ambry Mot. at 37, 43; Plfs' GBG Mot. at 32-33, 38. Ambry's contrary representations regarding its failure rate are subject to serious question, given its short time on the market and very small number of samples (1,000, as compared to Myriad's of over 1,000,000). *See infra* at II(C)(2)(a) and declarations cited therein. And, since both Defendants acknowledge that they are relying on the public database, their claims of significantly higher VUS rates similarly require close examination. Eggington Decl., ¶¶ 5-9. Additionally, while Ambry touts that its testing reports are superior because they purportedly provide more information, more information, in itself, is not necessarily a benefit. Any benefit depends on the accuracy of the information, and statistically insignificant data is frequently misleading and may be subject to misinterpretation, is potentially harmful to patients and counter to the public interest. Eggington Decl., ¶¶ 10-11.

2. Defendants Have Failed to Show that the Public Interest In Testing Is Not Fully Served by Myriad.

Defendants largely fail to address the authority holding that the statutory period of patent exclusivity "warrants weight in considering the public interest."[49] Instead, they rely upon

[49] While Defendants attempt to convert that inquiry into one regarding the desirability of patents pertaining to genetic innovation in general, that policy-based argument is inappropriate for consideration here, as set forth in Myriad's Objections to Evidence filed concurrently herewith.

argument and declarations, frequently from biased sources[50] claiming that the public interest is served by allowing Defendants to market their infringing tests. Defendants' assertions fail factually and legally.

a. Defendants' Assertions Regarding the Quality and Extent of Myriad's Test Offerings Are Incorrect.

Defendants attempt to take issue with Myriad's showing regarding its near-perfect accuracy rate and VUS rate of less than 3%, as contrasted with those of Defendants. Regarding accuracy rate, Ambry claims that it has "analytic sensitivity . . . greater than 99%", while Gene by Gene claims that its analytic sensitivity is "99% or greater." Defs' Opp. at 106-07. First, Ambry's allegations regarding its sensitivity rate should be viewed with caution, in light of the fact that it initially indicated on its website that its rate was 96-99%, then, a mere seven days later, changed that statement to 99%. Plfs' Ambry Mot. at 37. Now, it claims it to be even greater than 99%. Ambry's accuracy rate thus appears to be a moving target. Second, Ambry's assertions must also be viewed in light of the fact that it has only been on the market for a few short months, and has publicly announced only 1,000 reported cases, which likely does not constitute a sufficient database for a reliable percentage. http://www.ambrygen.com/brca-beyond; *see* Geier Decl., ¶ 29. Further, it is unclear how Gene by Gene is supporting its rate, given its assertion that it has not even entered the market. Defs' Opp. at 82. Myriad's rate, in stark contrast, is supported by data from over 1,000,000 patients and family members of patients tested. Ford Decl., ¶ 6.

[50] For example, Dr. Swisher is a Professor in the Department of Obstetrics and Gynecology at the University of Washington, an entity that Defendants have frequently referred to as another competitor of Myriad's in the BRCA 1 and BRCA 2 market. Furthermore, at least two of Defendants' declarants, Robert Nussbaum and Ellen Matloff, ordered testing from Myriad mere weeks ago, thus calling into question their perjorative assertions regarding the quality and/or accuracy of those tests.

Regarding their rate of variants of unknown significance, Defendants acknowledge that they "are tapping into a number of existing public databases of BRCA1/2 data", but nonetheless assert a VUS rate of 4.5% with respect to Ambry (and 12-13% for Gene by Gene). Defs' Opp. at 105. However, as Dr. Eggington explains, there are many reasons to be skeptical of this figure, or to conclude that it cannot fairly be compared to Myriad's robust figure. Eggington Decl., ¶ 9. Among other things, the ***best*** expected VUS rate for labs using publicly available data with roughly 2,000 patient samples (double that of Ambry) are expected to be much higher than 4.5%. *Id*., ¶ 9(a). Thus, Ambry's figure is subject to serious question, and, at best, is likely reflective of the fact that Ambry's limited number of samples does not reflect the same testing population as Myriad's (*i.e*., all comers). *Id*., ¶ 9(b).[51]

Myriad, in contrast, employs a detailed and highly tested methodology for classifying variants which it has honed over its years of experience. *Id*., ¶¶ 8, 13. *See also* Geier Decl., ¶¶ 39, 29 (stating "[b]ecause of Myriad's many years of experience in testing, they have by far the largest database of test results, and therefore the least chance that any given mutation identified will have uncertain consequences"; as compared with Ambry's cited VUS rate which likely has not been validated since "they have only been doing testing for a few weeks"); Declaration of Jane M. Porretta, M.D., FACS ("Porretta Decl."), ¶ 7 ("I trust Myriad's classification efforts when making life-altering clinical recommendations for my patients."); Declaration of Adam A. Ofer, M.D., FACOG ("Ofer Decl."), ¶ 7 (Myriad's "very robust variant reclassification program

[51] Furthermore, it is likely that much of Ambry's data reflects testing of patients who were previously tested with *BRACAnalysis* and received a result of "No Mutation Detected." Indeed, providers have reported to Myriad that Ambry frequently requests the patient's Myriad test report. This test population likely is heavily skewed for patients who do not have a BRCA1/2 variant, which necessarily affects Ambry's VUS rate. *Id*., ¶ 9(b).

. . . has brought the rate down from the roughly 20% which would be expected to my experienced rate of 1-2%"); Declaration of Randall W. Burt. M.D. ("Burt Decl."), ¶ 6.

Nor can there be any real dispute regarding the quality of BRACAnalysis®. Defendants characterize the test as "substandard" absent specifics (other than their claims regarding the scope of the test *vis a vis* integrated panels and large rearrangements, which are discussed below). In fact, the medical community has been outspoken in its regard for the high quality of Myriad's tests. *See* Declaration of Richard P. Frieder, M.D., FACOG ("Frieder Decl."), ¶ 13 ("I have always been 100% confident in the analytic test quality that Myriad provides. They are renowned throughout the industry for the highest level of quality control, and for this reason were asked by the federal government to participate in the DNA identification of victims in the 2001 World Trade Center tragedy. I have never encountered a patient, physician, genetics counselor, or academic center that lacked confidence in their results. In an area of medicine in which absolute confidence is necessary due to the life-changing dependency upon subtle genetic results, Myriad maintains the highest levels of sensitivity and specificity in the industry.") *See also* Declaration of Jennifer J. Tittensor, M.D., FACS ("Tittensor Decl."), ¶ 5; Declaration of Marra S. Francis, M.D., FACOG ("Francis Decl."), ¶ 4; Declaration of Jay S. Cohen, M.D., FACOG ("Cohen Decl."), ¶ 4; Burt Decl., ¶ 5.

Defendants' criticisms regarding the scope of Myriad's tests are similarly incorrect. Defendants make the sweeping assertion that patients and health care providers "prefer Defendants' testing over Myriad's testing." Defs' Opp. at 98. Notably, Defendants cite no specific testimony to this effect, but instead rely upon the supposed distinction that Ambry offers a multi-gene panel (that includes BRCA1 and BRCA2 testing along with tests for other genes associated with hereditary cancer risk) and comprehensive testing in a single test (*i.e.*, for point

mutations and large rearrangements). *Id*. at 99-100.[52] These supposed "distinctions" fail upon examination. Regarding the multi-gene panel, it is incorrect to imply that patients are disserved simply because Ambry tests for non-BRCA genes. This is equivalent to arguing that an M.R.I. test is inferior because it does not also include an x-ray. Indeed, before it began infringing Myriad's patents-in-suit, Ambry's BreatNext panel was marketed to patients who had received a negative result from Myriad for mutations in additional genes.[53] It strains reason for Ambry to assert that maintaining this status quo somehow harms patients.

Furthermore, Defendants' claim that providers or patients who had to order separate tests for the BRCA genes and other genes were unfairly burdened (*see* Declaration of Elizabeth Swisher, M.D. (Dkt. #'s 59 and 42) at ¶ 105; Declaration of Elizabeth Chao (Dkt. #'s 56 and 46) at ¶¶ 23-25), does not accurately reflect current market conditions and thus have no bearing upon the instant Motion. As explained in its Motion, Myriad plans to bring to market its MyRisk™ Hereditary Cancer™ panel later this year [with a limited launch now expected in September],

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[52] While Defendants refer to cases declining to enjoin infringing tests and products in medical settings (Defs' Opp. at 98), those cases are inapposite. In each of those cases an injunction would have caused specific and harmful effects to public health because the device sought to be enjoined was either clearly superior to the patentee's device, would had been seriously disruptive to surgical procedures, or would have ceded ground in the battle against life-threatening conditions. Such considerations are absent here. Ambry's test is not superior to Myriad's, has not yet become a widely-used or known option in the molecular diagnostics field, and enjoining Ambry's test would not cause any added risk to patients, or to the fight against cancer because all of those interests are being met by Myriad's products and have been for some time.

[53] *See* http://www.pennstatehershey.org/web/cancer/patientcare/geneticcounseling/news: "Recently, new genetic testing has become available that provides simultaneous analysis of multiple genes that contribute to an increased risk for various types of cancer. Ambry Genetics has released four next-gen sequencing panels including BreastNext, OvaNext, ColoNext and CancerNext. Each panel focuses on a targeted group of genes that are related to the cancer type depicted by the panel name. For example, BreastNext examines breast cancer susceptibility genes whereas ColoNext examines genes that contribute to an increased risk for colon cancer. **Please note that the BreastNext panel is primarily for patients who have previously tested negative for BRCA1 and BRCA2 mutations.** If you are interested in learning more about this testing, please contact your cancer genetic specialist to discuss in further detail."

which will offer testing of 25 different genes in six different cancers, including the BRCA genes. Plfs' Ambry Mot. at 39; Plfs' GBG Mot. at 35. Thus, this panel will offer patients the option of a full test for genetic cancer predisposition. Defendants acknowledge the same. *See* Defs' Opp. at 104 ("Myriad has announced that it, too, finally intends to use next-generation sequencing and offer a multi-gene panel"). And, as set forth in the Geier Declaration, the fact that Myriad has taken somewhat longer to bring its integrated panel to the marketplace is reflective of Myriad's appropriately conservative philosophy perhaps best described by the maxim that "It is better to be right than to be fast." Geier Decl., ¶ 44.[54]

Defendants' complaint that Myriad does not offer a single test for point mutations and large rearrangements fails for similar reasons. Defs' Opp. at 99-100; 104. In fact, Myriad offers Integrated *BRACAnalysis*® which includes detection of both point mutations and large rearrangements (which detect mutations that represent less than 5% of all demonstrable BRCA mutations). *See* Geier Decl., ¶ 34, 44. Additionally, the fact that Myriad has several test offerings allows healthcare providers to choose the test that, in the provider's professional judgment, is most appropriate for a patient. *See* Tittensor Decl., ¶ 6. Furthermore, due to guidelines issued by the National Comprehensive Cancer Network which provide that any patient qualified for BRCA testing should automatically be qualified for BART as well, BART is

[54] Ambry also fails to acknowledge the fact that its argument would result in an infringer being allowed to bundle infringing tests (BRCA1 and BRCA2) with noninfringing tests (such as those related to hereditary colon cancer) in order to avoid an injunction. Defendants cite no authority for the proposition that efficiency concerns can trump exclusive patent rights. Myriad's Motion does not attempt to preclude Defendants from offering any panel that does not incorporate infringing tests. As a result, any patient or healthcare provider preferring Ambry's non-BRCA tests over those offered by Myriad may continue to order such tests from Ambry (or any other supplier for that matter). Indeed, it is not difficult to imagine that if Myriad only offered its BRCA test in conjunction with other, non-patented hereditary cancer tests, Defendants would be claiming that Myriad was unfairly tying non-patented tests to its patented technology.

now widely accepted, almost universally covered, and automatically included in BRCA testing. Geier Decl., ¶¶ 36-37. *See also* Tittensor Decl., ¶ 6 (stating that Myriad offers the full range of testing for hereditary breast and ovarian cancer testing that is recommended by the industry guidelines).[55]

The fact that Myriad bills separately for point mutation and large rearrangement testing (Defs' Opp. at 100, 104) is of little moment. As Dr. Tittensor stated, she typically orders BRAC*Analysis*® which includes the *BRCA1* and *BRCA2* tests as well as large rearrangement analysis, but has the option of ordering BRACAnalysis® Large Rearrangement Test (BART) separately if she determines that is best for the patient based on her clinical experience and the medical society guidelines. *Id*., ¶ 7. This is an appropriate result that is by no means deleterious to the patient.

Finally, the supposition that patients are not able to obtain "an independent and meaningful second opinion" absent Defendants' tests is incorrect. First, as set forth in Myriad's Objections to Evidence, arguments regarding "second opinion testing" are not properly an issue for this Court, but are policy-based arguments best committed to the legislative branch. In fact, Congress has asked the U.S. Patent and Trademark Office to study this very issue and make recommendations back to Congress. In any event, however, the implication that Myriad does not allow second opinion testing is factually incorrect. Myriad does not and has not asserted its patents against anyone performing "second opinion" testing, and has publicly announced that it

[55] To the extent that Defendants criticize Myriad for not making its BART testing available sooner (even prior to medical society guidelines recommending such testing), the *Aria Diagnostics* court noted that the existence of, or absence of, medical society guidelines is a relevant factor in determining whether the public interest is being served. *See Aria Diagnostics*, -- F.3d --, 2013 WL 4034379 at * 8.

will continue this practice. Ford 2nd Decl., ¶ 6. Defendants have not and cannot make any showing to the contrary.[56]

b. Myriad's Test Offers Superior Access and Affordability, a Fact that Defendants Cannot Credibly Dispute.

Similarly, Defendants' tests do not offer greater "access and affordability." Defs' Opp. at 102-103.[57] To the contrary, Myriad has gone to great lengths not only to establish the market for insurance reimbursement of genetic predisposition cancer testing, but also to ensure that such testing is affordable for all patients. To that end, Myriad has not only developed a market of insurance reimbursement and secured and maintained in-network contracts with more than 530 private payors, ensuring that patients have the lowest possible out-of-pocket expense, it also has implemented four separate patient assistance programs. Ford 2nd Decl., ¶¶ 3 & 4. Defendants do not refute Myriad's showing that, over the past 5 years, more than 35,000 patients have received some form of financial assistance from Myriad. *Id*., ¶ 4*; see also* Francis Decl., ¶ 6 (regarding her work at free clinic for women who are ineligible for any form of private or public insurance, "I am always able to get those women who meet criteria tested for free through Myriad's Financial Assistance Program."). Similarly, Defendants do not counter that Myriad's efforts with third-party payors have led to enviable results; greater than 99% of BRACAnalysis® tests ordered have some insurance reimbursement, approximately 80% of patients who receive the test pay nothing, and the average out of pocket cost is less than $100. *Id*. at ¶ 4. While Defendants

[56] Furthermore, testing to confirm a deleterious mutation is available at a number of institutions as well as the largest reference laboratory in the United States to whom Myriad licensed the right to do single site testing. *See* http://investor.myriad.com/releasedetail.cfm?ReleaseID=771232 ("While we are confident that Myriad offers the highest quality genetic tests in the world, we also support patients' rights to seek second opinion tests from any of the many laboratories conducting BRCA testing for the purpose of confirming the Myriad test result.").

[57] In urging the discounted price of their tests, Defendants fail to counter the authority set forth by Myriad which holds that the public interest is not necessarily advanced by cheaper infringing products. *Abbott Labs*, 544 F.3d at 1362.

allege examples of women who "chose to pay for Ambry's testing out of pocket," they fail to show that such occurrence is significant rather than isolated, anecdotal instances when compared with the vast number of individuals who have benefited from Myriad's efforts in establishing insurance reimbursement and providing financial assistance.

Furthermore, as demonstrated by a number of Myriad's declarants, insurance coverage of BRACAnalysis® is currently very broad and reaches most patients tested. Porretta Decl., ¶ 5; Francis Decl., ¶ 6; Geier Decl., ¶17; Frieder Decl., ¶ 15; Ofer Decl., ¶ 8; Declaration of William J. Harb, M.D., FACS ("Harb Decl."), ¶ 7. This is largely due to Myriad's efforts. Geier Decl., ¶ 16 ("Myriad has led the charge to get medical insurance companies to understand the importance of these syndromes, and ultimately to convince them to cover the costs of testing. As a result, almost all insurers now cover testing, including Medicare and many Medicaid programs."); Frieder Decl., ¶ 15 ("Over the last 15 years, the massive conversion of the insurance industry to cover this critically important hereditary cancer testing is singularly attributable to Myriad's diligence in providing information generated in scientific research to policy makers within the insurance industry."). Furthermore, Myriad has gone well out of its way over that period to interact directly with insurers, thus removing that burden from clinicians and providers and smoothing the way for patients. Tittensor Decl., ¶ 7; Porretta Decl., ¶¶ 4-5; Burt Decl., ¶ 7. In sum, there can be no serious question that Myriad has dedicated extraordinary effort to offering an affordable, accessible test during its time in the market, and has achieved considerable success in doing so.

c. <u>Defendants' Remaining Assertions Are Largely Policy-Based and Irrelevant, and in Any Event Ignore Myriad's Extensive Contributions to the Market.</u>

Defendants' assertions regarding the alleged "hindering of innovation" they urge is associated with patents on genetic innovations (Defs' Opp. at 101-102; 107-109) also fail upon

examination. At the outset, all of these arguments pertain to the desirability of patents relating to genetic testing, and the purported effect of such patents. These assertions are grounded entirely in public policy considerations. For the reasons discussed in Myriad's concurrently filed Objections to Evidence, they have no bearing upon any issue to be considered by the Court in conjunction with Myriad's motion for injunctive relief. Not only are they irrelevant, they run directly afoul of the Federal Circuit Court of Appeal's directive in *Ass'n for Molecular Pathology v. United States Patent & Trademark Office*, that "disapproving of patents on medical methods and novel biological molecules are policy questions best left to Congress." 689 F.3d 1303 at 1324-25 (Fed. Cir. 2012), *aff'd in part, rev'd in part*, *Ass'n for Molecular Pathology v. Myriad Genetics, Inc., et. al*., 133 S.Ct. 2107 (2013).

Furthermore, while Defendants are critical of the notion that patents such as Myriad's incent innovation, there are many voices on the other side of that debate. *See* Mangum Decl., Exh. E (Brief of Drs. Larry Geier, William Harb, Adam Ofer, and Donald Aptekar as Amici Curiae in Support of Respondents); Exh. F (Brief for the Philadelphia Intellectual Property Law Association as Amicus Curiae in Support of Respondent Myriad Genetics, Inc.). In short, there is no basis for this Court to credit the policy arguments of Defendants (or their amici) over similar arguments on the other side of those same issues.[58] Additionally, Myriad has publically pledged to refrain from asserting its patents against any entity performing non-commercial research, thus underscoring its commitment to using its decades of work and research to further the interests of the medical and academic communities in continued advancements. *See*

[58] For similar reasons, Defendants' assertions regarding the proprietary nature of Myriad's database should not be considered. As patentee, Myriad is entitled to exploit the benefits of its invention, and any argument to the contrary is best made to Congress, not this Court. *See* Geier Decl., ¶ 42.

http://investor.myriad.com/releasedetail.cfm?ReleaseID=771232 ("Already, more than 10,000 scientific papers have been published on the BRCA genes, ranking them among the most researched genes in history. We are committed to advancing scientific knowledge even further, and Myriad will continue to encourage and support academic research studies conducted on the BRCA genes.").

Finally, in its position as the primary provider of BRCA1 and BRCA2 tests, Myriad has benefitted the market by acting with a high corporate ethos, including its extended efforts directed toward educating the medical community about hereditary cancer predisposition testing. Frieder Decl., ¶ 11 ("I continue to be impressed with their social conscience, reputable business practices, and acquisition of the most talented individuals with whom I have every associated"); Geier Decl., ¶¶ 23-24; Porretta Decl., ¶ 3; Francis Decl., ¶¶ 8, 10; Ofer Decl., ¶ 4; Cohen Decl., ¶ 6. This evidence provides yet another reason why Defendants' policy arguments (even if they were in any way relevant, which they are not) are flawed.

CONCLUSION

Because Myriad has more than met the standard for issuance of a preliminary injunction, its Motion should be granted.

Dated: August 30, 2013.

Respectfully submitted,

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CERTIFICATE OF SERVICE

On this 30th day of August 2013, I certify that I electronically filed the foregoing **PLAINTIFFS' REPLY IN SUPPORT OF MOTION FOR PRELIMINARY INJUNCTION** with the Clerk of Court using the CM/ECF system that will send an electronic notification to counsel of record for all of the parties.

/s/ David G. Mangum